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[54] ORAL SUSTAINED RELEASE ACETAMINOPHEN FORMULATION AND PROCESS

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[57] ABSTRACT

An acetaminophen-sustained release tablet or tablet layer is formed by making a wet granulation, using Povidone (PVP) in water or alcohol-water as the granulating fluid which is mixed with acetaminophen, hydroxyethyl cellulose, a wicking agent e.g. microcrystalline cellulose, then drying and milling the granulation and blending with dry powdered erosion promoter, e.g. pregelatinized starch, wicking agent, lubricant e.g. magnesium stearate and glidant e.g. silicon dioxide, and compressing the resultant granulation, which upon administration results in a slow release of the acetaminophen.

17 Claims, No Drawings

ORAL SUSTAINED RELEASE ACETAMINOPHEN FORMULATION AND PROCESS

This invention relates to a sustained release form of acetaminophen, and is more particularly concerned with an acetaminophen-containing matrix formed from granulations of acetaminophen mixed with inactive powered excipients plus hydroxyethyl cellulose (HEC) using an aqueous solution of Povidone U.S.P. (polyvinylpyrrolidone—PVP) as the granulated agent, which granulations are dried, milled, blended with additional inactive powdered excipients, and then compressed into a tablet, and to the process of making the acetaminophen-containing matrix in a manner so that the rate of release of acetaminophen can be varied or controlled.

BACKGROUND OF PRESENT INVENTION

Acetaminophen (APAP) is a well-known analgesic and antipyretic drug. In the United States, it is available for non-prescription over-the-counter sale in conventional liquid, suppository, capsule, tablet and caplet dosage forms. The tablet and caplet dosage forms typically contain 325 mg acetaminophen as "regular strength" or 500 mg as "extra strength". Normally, regular strength tablets or caplets are taken as one or two every four hours, and the extra strength tablets or caplets are taken as one or two every six hours. Ideally, it would be desirable to extend th dosing interval while maintaining the initial plasma concentrations achievable with conventional tablets or caplets. This would provide immediate and extended therapeutic analgesic or antipyretic effect and reduce the number of doses necessary, thereby making therapy more convenient. A way to do this has now been found, using the present invention, whereby two tablets or caplets each containing 650 mg acetaminophen can be formulated to provide both immediate release and sustained release or sustained release alone such that the dosing interval can be extended to at least eight (8) hours. In addition, the quantity (amount) of the sustained release matrix can be adjusted up or down to produce tablets for sustained release that have more or less than 650 mg of acetaminophen. For example, a tablet containing 500 mg of acetaminophen can be manufactured from the same composition by simply decreasing the size and weight of the final tablet by a multiple of 10/13. The present invention can be used to obtain any desired sustained release acetaminophen tablets of different dosages, e.g. a 500 mg sustained release tablet which results in lower blood plasma levels over eight hours, than with the 650 mg tablet, and desired longer or shorter time periods, e.g. twelve hours are possible. From a practical standpoint eight (8) hours might be the most desired interval. The matrix of the present invention can be used to make acetaminophen sustained release pharmaceutical preparations in compressed tablet form. The matrix materials used are compressed into a shaped tablet form. The term "tablet" as used herein includes tablets of any shape, and includes caplets, which are tablets having a capsule shape. The tablets may be coated with a pharmaceutically acceptable coating material or have pharmaceutically acceptable coloring added to the composition prior to compression.

PRIOR ART

Both hydroxyethyl cellulose (HEC) and polyvinyl pyrrolidone (PVP) have been used in pharmaceutical compositions, such as tablets, including sustained release compositions. However, the materials have not been used in the same way for the same purposes in a sustained release acetaminophen tablet composition. In U.S. Pat. No. 4,189,469 the examples show pharmaceutical compositions containing a xanthine as the active ingredient together with hydroxyethyl cellulose, PVP, and certain excipients. However, no wicking agent or erosion promoting agent is used there, so that the method of obtaining the sustained release affect is different in Applicant's invention. The ratio of drug to hydroxyethyl cellulose used is much higher in Applicant's sustained release formulations. Also, the reference does not refer to the use of wet granulation techniques which are required in Applicant's invention.

U.S. Pat. No. 4,264,573 teaches the use of PVP but does not teach the use of hydroxyethyl cellulose. It is typical of the many formulations for slow release via controlled surface erosion which are known in the prior art.

SUMMARY OF THE INVENTION

The present invention, in its process aspect is directed to the process of preparing an acetaminophen-sustained release shaped and compressed tablet characterized by a slow release of the acetaminophen upon administration comprising the following steps:

(A) forming a granulating agent by dissolving 5–25 parts by weight povidone in water or in an alcohol-water mixture;

(B) blending together the following ingredients in dry powder form;

Ingredient	Parts by Weight
Acetaminophen	325
Hydroxyethyl Cellulose	5–25
wicking agent e.g. Microcrystalline Cellulose	5–25

(C) adding the granulating agent from Step A to the blended powders from Step B, and mixing in a high shear granulator to form a wet granulation;

(D) drying the wet granulation of Step C;

(E) milling the dried granulation from Step D;

(F) thoroughly blending the milled dried granulation from Step E with the following ingredients in dry powder form;

Ingredient	Parts by Weight
erosion promoter e.g. Pregelatinized Starch	1–15
wicking agent e.g. Microcrystalline Cellulose	5–45
libricant e.g. Magnesium Stearate	0–10
glidant e.g. Colloidal Silicon Dioxide	0–5

(G) compressing the final granulation from Step F into a tablet or tablet layer.

In its product aspect the present invention is directed to a shaped and compressed sustained release therapeutic composition comprising acetaminophen as the therapeutically-active medicament and granulating agent and excipients combined into a matrix, characterized by a slow release of the acetaminophen medica-

ment upon administration, wherein the graulating agent and excipients includes a combination of two polymers, hydroxyethyl cellulose and povidone, and wherein the total amount of ingredients other than acetaminophen in the sustained release matrix may, in the most preferred embodiments, be less than fifteen (15) percent of the weight of said shaped and compressed composition.

The preferred tablets of this invention include a shaped and compressed acetaminophen sustained release tablet made by wet granulating the Active & Excipients ingredients of Part I with the Granulating Agent of Part II, drying and milling the resultant granulations, and then blending with the Excipients of Part III and compressing into a tablet, wherein the ingredients of Parts I, II and III comprise the following:

	Ingredient	Parts by Weight
Part I	Active & Excipients	
	Acetaminophen	325
	Hydroxyethyl Cellulose	5-25
	Microcrystalline Cellulose	5-25
Part II	Granulating Agent	
	Povidone	5-25
	Water or Alcohol-Water	q.s
Part III	Excipients	
	Pregelatinized Starch	2-15
	Microcrystalline Cellulose	5-45
	Magnesium Stearate	0-10
	Colloidal Silicon Dioxide	0-5

The invention preferably is utilized in the form of a bi-layer tablet containing both an immediate release layer and a sustained release layer.

In addition to the hydroxyethyl cellulose and PVP polymers discussed above which are "Matrix Binding Agents", the commonly used excipients which are granulated with the acetaminophen must include a "wicking agent" (to wick fluids into the matrix) such as microcrystalline cellulose, and an "erosion promoter" such as pregelatinized starch. Additional excipients which are added to the granulated and dried ingredients include a wicking agent such microcrystalline cellulose, an erosion promoter such as pregelatinized starch, and optionally a lubricant such as magnesium stearate and a glidant such as colloidal silicon dioxide. The use of a lubricant is preferred, while the use of a glidant is possible but not usually needed.

DETAILED DESCRIPTION OF THE INVENTION

The acetaminophen sustained release matrix pharmaceutical tablets of the present invention are made by adding granulating agent to a dry powder blend of active drug and inactive excipients to form wet granulations, which are then dried and finely divided, e.g. by milling the dried granulations into a finer powder form, then blending with additional inactive powdered excipients and compressing into tablets. Tablets can be readily manufactured using conventional tabletting equipment.

The tablets of the present invention have novel and advantageous features. A primary advantage is that the tablets are bioerodible when swallowed, that is, no insoluble tablet shaped device remains to be excreted or removed from the body after acetaminophen is depleted from the tablet. The acetaminophen sustained release matrix uses hydroxyethyl cellulose (Hydroxyethyl Cellulose NF) and povidone (Povidone USP) (Plasdone ® K29/32) (PVP) as the Matrix Binding Agents for obtaining the sustained release effect. This combination of two well-known pharmaceutically acceptable polymers, in the relative proportions here used and in the manner used is believed to be a major novel feature of the present invention. In the most preferred embodiments of the invention, the amount of hydroxyethyl cellulose used is on the general order of four percent or less of the amount of acetaminophen, while the amount of povidone is on the general order of four percent or less of the amount of acetaminophen used. This means the acetaminophen sustained release matrix of the present invention is capable of producing dosage forms having very high drug/matrix binding agent ratios. This results in reducing the size or number of tablets needed, making the product easier to swallow, less expensive and more desirable to the consumer.

Another advantage of this invention is that the rate of matrix erosion when the tablet is swallowed can be modified so that the degree and/or length of the sustained release effect of the matrix can be easily modified by simply altering the levels of the other excipients, aside from the hydroxyethyl cellulose and the povidone (PVP). Hence, the rate at which acetaminophen is released from the tablet and subsequent absorption from the gut into the bloodstream can be modified to match the desired blood plasma concentration versus time profile.

The acetaminophen sustained release matrix of the present invention can be used alone as a shaped and compressed tablet (tablet can be any shape such as oval, round, caplet or spherical), or as part of a multi-layered tablet containing an immediate or quick-release layer to elevate the blood levels of acetaminophen quickly and also containing a sustained release portion to maintain the elevated blood level. Hence, the present invention can be used to prepare tablets with two or more layers, each with a significantly different release rate of the same component, or to prepare tablets of different components where a combination of drugs is desired.

The acetaminophen sustained release matrix, in our currently preferred embodiments, contains approximately three percent hydroxyethyl cellulose and approximately three percent povidone (PVP), with the balance consisting of various pharmaceutically acceptable, common excipients. The matrix tablets or tablet layers of the present invention have a very high drug-to-excipients ratio on the order of 85 percent acetaminophen to 15 percent excipients by weight. This results in a drug to total matrix weight ratio of approximately 1:1.2.

As discussed, the hydroxyethyl cellulose and PVP polymers are Matrix Binding Agents. The additional commonly used excipients that are granulated with the acetaminophen include a Wicking Agent (to wick fluids into the matrix) such as microcrystalline cellulose. Additional excipients that are added to the granulated and dried ingredients include a wicking agent such as microcrystalline cellulose, an Erosion Promoter such as pregelatinized starch, and a lubricant such as magnesium stearate.

For each of the ingredients used in the sustained release matrix of the present invention, aside from the acetaminophen, the hydroxyethyl cellulose, and the povidone (PVP) there exists less preferred alternative or equivalent materials which could be used in its place. The following Table I lists each of the various preferred ingredients, the purpose of the ingredient, the preferred weight of such preferred ingredient, the usable weight

range of the preferred ingredient, other less preferred alternatives or equivalents which can be substituted for the preferred ingredient, the preferred weight of such alternate ingredient and the usable weight range of such alternate ingredient needed for the sustained release layer containing 325 mg of acetaminophen. For matrices (tablets or caplets) of a higher or lower level of acetaminophen, the amounts of ingredients and their ranges would be proportionately increased or decreased.

The ingredients are listed in Table I under Part I Active & Excipients, Part II Granulating Agent, Part III Excipients, since they are used in this manner in the process by which the tablets of the present invention are made.

The preferred process which is utilized from form the most preferred acetaminophen sustained release matrix of the present invention is to mix together the dry powdered active drug, acetaminophen, the dry powdered matrix binding agent, hydroxyethyl cellulose, and the dry powdered wicking agent, microcrystalline cellulose in a mixer/granulator. A granulating fluid or solution is formed by dissolving povidone into water at a ratio of 19.1 grams of povidone to 100 grams of water. The resultant granulating agent is sprayed onto the above admixed powders while they are being mixed in the mixer/granulator so as to form a wet granulation. The wet granulation thus obtained is dried and milled. At this point, a small amount of dry powdered excipients such as pregelatinized starch, microcrystalline cellulose and magnesium stearate are added, and mixed with the milled granulations, after which they are compressed thereby forming the sustained release matrix.

TABLE I

SUSTAINED RELEASE ACETAMINOPHEN MATRIX

Preferred Ingredient	Purpose	(mg) Wt. per Tablet	(mg) Range	Alt. or Equiv.	(mg) Wt. per Tablet	(mg) Range
Part I - Active & Excipients						
Acetaminophen, USP	Active	325	—	—	—	—
Hydroxyethyl Cellulose NF (Natrosol®/250L)	Matrix Binding Agent	10.7	5-25	—	—	—
Microcrystalline Cellulose NF, (Avicel® PH 101,102,103,105)	Wicking Agent	10.7	5-25	Powdered Cellulose (Solka Floc®)	10.7	5-25
Part II - Granulating Agent						
Povidone, USP (Plasdone® K29/32)	Matrix Binding Agent	10.7	5-25	—	—	—
Purified Water, USP	Solvent	q.s water-alcohol (up to 50%)				
Part III - Excipients						
Microcrystalline Cellulose USP(Avicel® PH 101,103,103,105)	Wicking Agent	15.0	5-45	Powdered Cellulose (Solka Floc®)	15.0	5-45
Pregelatinized Starch, NF (corn, wheat, or potato source)	Erosion Promoter	5.0	2-15	Starch NF (corn, wheat or potato) or rice starch,	5.0	5-10
				Sodium Starch Glycolate NF(Explotab®)	3.0	1-10
				Croscarmellose Sodium NF (Ac Di Sol®)	3.0	1-10
				Crospovidone NF(Povidone®XL)	3.0	1-10
Magnesium Stearate NF	Lubricant	5.0	0-10	Stearic Acid NF	5.0	5-10

EXAMPLE I

Acetaminophen Sustained Release Bi-Layer Tablet

This example illustrates a bi-layer tablet in which there is both an immediate release layer and a sustained release layer. The immediate release layer is analogous in composition and manufacturing procedure to currently available over-the-counter acetaminophen non-sustained release tablets. It is the sustained release layer that utilizes the matrix of the present invention. The acetaminophen content of the entire tablet is 650 mg.

The bi-layer tablet uses the following ingredients:

Ingredient	mg/Tablet
A. Immediate Release Layer	
Part I - Active and Excipients	
Acetaminophen, USP	325.0 mg
Powdered Cellulose, NF	42.3 mg
Pre-gelatinized Starch, NF	16.0 mg
Part II - Granulating Agent	
Starch, NF	26.0 mg
Purified Water USP	q.s.
Part III - Excipients	
Sodium Laurel Sulphate, NF	0.75 mg
Magnesium Stearate, NF	2.0 mg
Total	412.05 mg
B. Sustained Release Layer	
Part I - Active and Excipients	
Acetaminophen, USP	325.0 mg

-continued

Ingredient	mg/Tablet
Hydroxyethyl Cellulose, NF (Natrosol® 250L)	10.7 mg
Microcrystalline Cellulose, NF (Avicel® PH 101)	10.7 mg
Part II - Granulating Agent	
Povidone, USP (Plasdone® K29/32)	10.7 mg
Purified Water, USP	q.s.
Part III - Excipients	
Microcrystalline Cellulose, USP (Avicel® PH 101)	15.0 mg
Pregelatinized Starch, NF (Starch 1500)®	5.0 mg
Magnesium Stearate, NF	5.0 mg
Total	382.1 mg
Total Tablet Weight	794.15 mg

The above ingredients are utilized to make a bi-layer tablet, by the following working directions:

Working Directions

A. Immediate Release Layer

1. Weigh the components of Part I and add them to the bowl of a fluid bed granulator (Aeoromatic).
2. Prepare the granulating agent (Part II) by adding the Purified Water to a processing tank (approximately 15 grams water for each gram of Starch NF). Slowly mix in the starch and heat the mixture until the temperature reaches 82° C.–84° C.
3. With the components of Part I in a heated fluidized state (inlet air temperature 75° C. to 85° C.), spray the granulating agent onto the powders.
4. After all the granulating agent has been sprayed, dry the granulated powders to a moisture content of 1.4–1.9% as determined by loss on drying (e.g. Computrac).
5. Sieve the dried granulation (e.g. Glatt Quick Sieve: Stator No. 3, Screen No. 1.5 mm, 1000 RPM). Other machines such as Fitzpatrick Communition Mill can be used.
6. Blend the sieved and dried granulation with the powders of Part III using a suitable mixer such as a twin-shell, ribbon or planetary mixer.

B. Sustained Release Layer

1. Weigh the components of Part I and preblend in a high shear mixer (Fielder: impeller speed of approximately 250 RPM for 1 minute).
2. Prepare the granulating agent (Part II) by dissolving the Povidone USP in th Purified Water USP (a ratio of 19.1 grams of povidone to 100 gm of water).
3. Spray the granulating agent at a rate of 400 ml/min onto Part I in the high shear mixer. Granulate the mixture for one minute after the addition of Part II (Fielder: impeller speed of approximately 3000 RPM).
4. Remove the completed wet granulation from the high shear mixer and load it into the product bowl of a fluid bed apparatus (e.g. Aeromatic or Glatt). With an inlet air temperature of approximately 60° C., dry the granulation to a moisture level of 2.0 to 2.5% as determined by loss on drying (e.g. Computrac). The wet granulation can also be dried on trays in drying ovens.
5. Sieve the dried granulation (Glatt Quick Sieve: 1.5 mm Screen, Stator No. 3, 395 RPM). Other machines such as a Fitzpatrick Communition Mill can be used.
6. Blend the sieved and dried granulation with the powders of Part III using a suitable mixer such as a twin-shell, ribbon or planetary mixer.

C. Compression of Tablets or Caplets

1. Load the granulation of the immediate release layer into one hopper and the granulation of the sustained release layer into the second hopper of a bi-layer tableting machine (e.g. Stokes Versapress). Compress tablets using 0.749×0.281×0.060 extra deep concave capsule shaped tooling (Tablet Tooling of other shapes such as oval or round can also be used). The sustained release layer has a target weight of 382.1 mg and the immediate release layer has a target weight of 412.05 mg. Ideal tablet hardness immediately after compression is 7–12 Kp.

The bi-layer tablets of Example I were tested in twelve adult male human subjects and compared to non-sustained release (immediate release only) tablets in a cross-over design. Two tablets of Example I, which contained 1300 mg of acetaminophen, were dosed at time=0 hour. The non-sustained release tablets, each containing 500 mg acetaminophen were dosed as two tablets (1000 mg acetaminophen) also at time=0 hour. Subjects were fasted at least 8 hours prior to administration of the dose. Blood samples were taken from each subject at 0, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours. Plasma was separated from the blood and the concentration of acetaminophen in each sample was determined. The results are shown numerically in Tables 2a and 2b. The results show that two bi-layer tablets of Example I, when compared to two tablets of non-sustained release acetaminophen (1000 mg dose), achieve the following: comparable rate of absorption: comparable maximum plasma concentration; and comparable extent of absorption (AUC or area under the curve) when adjusted for dose. Theoretically, the 1300 mg dose should provide 130% of the AUC of the 1000 mg dose. The results from Tables 2a and 2b show comparable extents of absorption by the following calculation: (64.3 mcg/ml divided by 49.5 mcg/ml)×100%=130%.

The tablets of Example I provide the opportunity to dose 30% more acetaminophen in a more convenient manner by extending the dosing interval to at least eight hours.

TABLE 2a

Sustained Release Acetaminophen 650 mg bi-layer tablets. (Example I) Average Plasma Concentration Levels of Acetaminophen (mcg/ml) in twelve subjects after administration of two tablets (1300 mg). Average AUC equaled 64.3 mcg/hr.

	TIME (HOURS) POST DOSING								
0	1.0	1.5	2.0	3.0	4.0	6.0	8.0	10.0	12.0
Average (mcg/ml)									
0	12.5	12.8	11.9	10.0	7.5	4.4	2.6	1.6	1.0

TABLE 2b

Non-sustained Release Acetaminophen 500 mg tablets. Average Plasma Concentration Levels of Acetaminophen (mcg/ml) in twelve subject. Average AUC equaled 49.5 mcg/hr.

	TIME (HOURS) POST DOSING								
0	1.0	1.5	2.0	3.0	4.0	6.0	8.0	10.0	12.0
Average (mcg/ml)									

TABLE 2b-continued

Non-sustained Release Acetaminophen 500 mg tablets. Average Plasma Concentration Levels of Acetaminophen (mcg/ml) in twelve subject. Average AUC equaled 49.5 mcg/hr.

	TIME (HOURS) POST DOSING							
0	1.0	1.5	2.0	3.0	4.0	6.0	8.0	10.0	12.0
0	12.1	11.4	10.0	7.3	5.3	2.9	1.8	1.1	0.6

EXAMPLE II

Acetaminophen Sustained Release Tablet Containing 650 mg of Acetaminophen in Matrix Form

This example illustrates an all-matrix (mono-layer) tablet in which there is only a sustained release layer. The working directions are analogous to the working directions for the sustained release layer described in Example I except that the amounts of all ingredients are proportionally increased such that the final tablet contains 650 mg acetaminophen. Tablets can be compressed using capsule, oval, round or other appropriately shaped tooling. The final target weight of the compressed tablet is 764.2 mg.

Ingredient		mg/Tablet
Part I - Active and Excipients		
Acetaminophen, USP		650.0 mg
Hydroxyethyl Cellulose, NF (Natrosol® 250L)		21.4 mg
Microcrystalline Cellulose, NF (Avicel® PH 101)		21.4 mg
Part II - Granulating Agent		
Povidone, USP (Plasdone® K29/32)		21.4 mg
Purified Water, USP		q.s
Part III - Excipients		
Microcrystalline Cellulose, NF (Avicel® PH 101)		30.0 mg
Pregelatinized Starch, NF (Starch 1500®)		10.0 mg
Magnesium Stearate, NF		10.0 mg
	Total	764.2 mg

EXAMPLE III

Acetaminophen Sustained Release Bi-layer Tablet Containing More than a total of 650 mg acetaminophen

This example illustrates a bi-layer tablet which is analogous to the tablet described in Example I, except all amounts of ingredients per tablet and final weight of the tablet are proportionally increased. The amount of the increase is theoretically indefinite, but one practical amount would be a 16⅔ mg increase in the amount of acetaminophen such that the total amount of acetaminophen in a tablet would be 666⅔ mg. Hence, if the tablets were dosed as two every eight hours, the maximum total amount of acetaminophen consumed in a 24 hours period would be 4 grams. The working directions for the immediate release layer and the sustained release layer are analogous to the working directions described in Example I. Tablets can be compressed using capsule, oval, round or other appropriately shaped tooling. For a tablet containing a total of 666.66 mg (an approximation of 666⅔ mg) acetaminophen, the sustained release layer has a target weight of 391.99 mg and the immediate release layer has a target weight of 422.65 mg.

Ingredient		mg/Tablet
A. Immediate Release Layer		
Part I - Active and Excipients		
Acetaminophen, USP		333.33 mg
Powdered Cellulose, NF		43.4 mg
Pregelatinized Starch, NF		16.4 mg
Part II - Granulating Agent		
Starch, NF		26.7 mg
Purified Water, USP		q.s.
Part III - Excipients		
Sodium Laurel Sulfate, NF		0.77 mg
Magnesium Stearate, NF		2.05 mg
	Total	422.65 mg
B. Sustained Release Layer		
Part I - Active and Excipients		
Acetaminophen, USP		333.33 mg
Hydroxyethyl Cellulose, NF (Natrosol® 250L)		11.0 mg
Microcrystalline Cellulose, NF (Avicel® PH 101)		11.0 mg
Part II - Granulating Agent		
Povidone, USP (Plasdone® K29/32)		11.0 mg
Purified Water, USP		q.s.
Part III - Excipients		
Microcrystalline Cellulose, NF (Avicel® PH 101)		15.4 mg
Pregelatinized Starch, NF (Starch 1500®)		5.13 mg
Magnesium Stearate, NF		5.13 mg
	Total	391.94 mg
	Total Tablet Weight	814.64 mg

EXAMPLE IV

Acetaminophen Sustained Release Bi-layer Tablet Containing Less Than a Total of 650 mg Acetaminophen

This example illustrates a bi-layer tablet which is analogous to the tablet described in Example I, except all amounts of ingredients per tablet and final weight of the tablet are proportionally decreased. One practical decrease in the amount of acetaminophen would be 150 mg such that the total amount of acetaminophen in a tablet would be 500 mg. The working directions for the immediate release layer and the sustained release layer are analogous to the working directions described in Example I. Tablets can be compressed using capsule, oval, round or other appropriately shaped tooling. For a tablet containing a total of 500 mg acetaminophen, the sustained release layer has a target weight of 293.89 mg and the immediate release layer has a target weight of 316.92 mg.

Ingredient		mg/Tablet
A. Immediate Release Layer		
Part I - Active and Excipients		
Acetaminophen, USP		250 mg
Powdered Cellulose, NF		32.5 mg
Pregelatinized Starch, NF		12.3 mg
Part II - Granulating Agent		
Starch, NF		20.0 mg
Purified Water, USP		q.s
Part III - Excipients		
Sodium Laurel Sulfate, NF		0.58 mg
Magnesium Stearate, NF		1.54 mg
	Total	316.92 mg
B. Sustained Release Layer		
Part I - Active and Excipients		

-continued

Ingredient	mg/Tablet
Acetaminophen, USP	250.0 mg
Hydroxyethyl Cellulose, NF (Natrosol® 250L)	8.23 mg
Microcrystalline Cellulose, NF (Avicel® PH 101)	8.23 mg
Part II - Granulating Agent	
Povidone, USP (Plasdone® K29/32)	8.23 mg
Purified Water, USP	q.s
Part III - Excipients	
Microcrystalline Cellulose, NF (Avicel® PH 101)	11.5 mg
Pregelatinized Starch, NF (Starch 1500®)	3.85 mg
Magnesium Stearate, NF	3.85 mg
Total	293.89 mg
Total Tablet Weight	610.81 mg

What is claimed is:

1. The process of preparing an acetaminophen-sustained release shaped and compressed tablet characterized by a slow release of the acetaminophen upon administration comprising the following steps:

(A) forming a granulating agent by dissolving 5–25 parts by weight of the total composition of Povidone in water or in an alcohol-water mixture;

(B) blending together the following parts by weight of the total composition of ingredients with sufficient acetaminophen to comprise 68 to 94 percent by weight of the total composition in dry powder form;

Ingredient	Parts by Weight
Hydroxyethyl Cellulose	5–25
wicking agent	5–25

(C) adding the granulating agent from Step A to the blended powders from Step B, and mixing in a high shear granulator to form a wet granulation;

(D) drying the wet granulation of Step C;

(E) milling the dried granulation from Step D;

(F) thoroughly blending the milled dried granulation from Step E with the following parts by weight of the total composition of ingredients in dry powder form:

Ingredient	Parts by Weight
erosion promoter	1–15
wicking agent	5–45
lubricant	0–10
glidant	0–5; and

(G) compressing the final granulation from Step F into a tablet or tablet layer.

2. The process of claim 1 wherein:

in Step A, when any alcohol is used, it is Alcohol USP or Dehydrated Alcohol USP or Methyl Alcohol USP or Isopropyl Alcohol USP, and is used in a quantity equal to or less than the water in the alcohol-water mixture;

in Step B the wicking agent used is Microcrystalline Cellulose or Powdered Cellulose;

in Step F the erosion promoter used is 2–15 parts by weight of either Pregelatinized Starch or Starch NF or rice starch, or is 1–10 Parts by Weight of Sodium Starch Glycolate or Croscarmellose Sodium or Crospovidone; the lubricant used is Magnesium Stearate or Stearic Acid; and, the Glidant used is Colloidal Silicon Dioxide or Fumed Silicon Dioxide.

3. The process of claim 2 wherein:

in Step A water is used;

in Step B the wicking agent used is Microcrystalline Cellulose; in Step F the erosion promoter used is Pregelatinized Starch; and the lubricant used is Magnesium Stearate.

4. The process of claim 3 wherein the specific ingredients and amounts used are:

Step A	Ingredient	Parts by Weight
A	water	q.s
	Povidone	10.7
B	Acetaminophen	325.0
	Hydroxyethyl Cellulose	10.7
F	Pregelatinized Starch	5.0
	Microcrystalline Cellulose	15.0
	Magnesium Stearate	5.0

5. The process of claim 4 wherein the Parts by Weight shown refer to milligrams per tablet.

6. A shaped and compressed sustained release therapeutic composition comprising Acetaminophen, a granulating agent and excipients combined into a matrix, characterized by a slow release of the Acetaminophen upon administration, wherein the granulating agent and excipients include Hydroxyethyl Cellulose and Povidone, and wherein the total amount of granulating agent and excipients is effective to bind the Acetaminophen in a sustained release solid matrix but is less than about 35 percent of the weight of said shaped and compressed composition.

7. A shaped and compressed Acetaminophen sustained release tablet made by wet granulating a sufficient amount of Acetaminophen to comprise from about 68 to 94 percent of the total composition with the Excipients of Part I and the Granulating Agent of Part II, drying and milling the resultant granulations, and then blending with the Excipients of Part III and compressing into a tablet, wherein the ingredients of Parts I, II and III comprise the following:

	Ingredient	Parts by Weight
Part I	Excipients	
	Hydroxyethyl Cellulose	5–25
	Microcrystalline Cellulose	5–25
Part II	Granulating Agent	
	Povidone	5–25
	Water or Alcohol-Water	q.s
Part III	Excipients	
	Pregelatinized Starch	2–15
	Microcrystalline Cellulose	5–45
	Magnesium Stearate	0–10
	Colloidal Silicon Dioxide	0–5

8. The tablet of claim 7 wherein the Parts by Weight refer to milligrams per tablet, and wherein the ingredients are present either in the weights indicated or in such weights multiplied by an appropriate fraction.

9. A composition according to claim 6 wherein the total amount of granulating agent and excipients is greater than about 6 but less than 15 percent of the total weight of said shaped and compressed composition.

10. A process of preparing an acetaminophen sustained release bi-layer tablet comprising a first layer of

immediate release and a second layer of sustained slow release of acetaminophen according to the steps of:

(A) preparing an immediate release layer comprising acetaminophen and pharmaceutically acceptable excipients; and

(B) preparing a sustained release layer comprising acetaminophen as the active ingredient according to the steps of:

(1) forming a granulating agent by dissolving about 5–25 parts by weight of the total sustained release layer of Povidone in alcohol or an alcohol-water mixture;

(2) blending together a sufficient amount of acetaminophen to comprise 68 to 94 percent of the total weight of the sustained release layer with the following ingredients in dry powder form in parts by weight of the total sustained release layer as indicated:

Ingredient	Parts by Weight
hydroxyethyl cellulose	5–25
wicking agent	5–25;

(3) adding the granulating agent from Step 1 to the blended powders from Step 2, and forming a wet granulation;

(4) drying the wet granulation of Step 3;

(5) milling the dried granulation Step 4;

(6) thoroughly blending the milled dried granulation from Step 5 with the following ingredients in dry powder form;

Ingredient	Parts by Weight
erosion promoter	1–15
wicking agent	5–45
lubricant	0–10
glidant	0–5; and

(C) combining and compressing the immediate release layer of Step A with the sustained release layer of Step B into a bi-layered tablet.

11. The process of claim 10 wherein:

in Step 1 the alcohol is alcohol USP, dehydrated alcohol USP, methyl alcohol USP or isopropyl alcohol USP; in Step 2 the wicking agent is microcrystalline cellulose or powdered cellulose; and

in Step 6 the erosion promoter is 2–15 parts by weight of the total sustained release layer and is either pregelatinized starch NF or rice starch, or is 1–10 parts by weight of the total sustained release layer and is sodium starch glycolate, croscarmellose sodium or crospovidone, the lubricant is magnesium stearate or stearic acid and the glidant is colloidal silicon dioxide or fumed silicon dioxide.

12. The process of claim 11 wherein:

in Step 1 the alcohol is alcohol USP;

in Step 2 the wicking agent is microcrystalline cellulose;

in Step 3 the wet granulation is formed by mixing in a high shear granulator; and

in Step 6 the erosion promoter is pregelatinized starch, the lubricant is magnesium stearate, and the glidant is colloidal silicon dioxide.

13. The process of claim 10 wherein the immediate release layer comprises a composition of the following ingredients:

acetaminophen; powdered cellulose; starch; pregelatinized starch; sodium laurel sulphate; and a granulating agent.

14. A shaped and compressed bi-layer therapeutic composition comprising acetaminophen in a first immediate release layer and a second sustained release layer wherein the immediate release layer comprises acetaminophen and pharmaceutically acceptable excipients and the sustained release layer comprises acetaminophen, a granulating agent and excipients combined into a matrix, wherein the granulating agent and excipients of the sustained release layer include hydroxyethyl cellulose and povidone, and wherein the total amount of said granulating agent and excipients is effective to bind the acetaminophen in a sustained release solid matrix but is less than about 32 percent of the weight of the sustained release layer of said shaped and compressed bi-layer composition.

15. The therapeutic composition of claim 14 wherein the immediate release layer comprises acetaminophen; powdered cellulose; starch; pre-gelatinized starch; sodium laurel sulphate; and a granulating agent.

16. The therapeutic composition of claim 14 wherein the amount of granulating agent and excipients is greater than about 6 percent but less than about 15 percent of the total weight of the sustained release layer of said shaped and compressed bi-layer composition.

17. A shaped and compressed bi-layered immediate release layer and sustained release layer acetaminophen tablet made by combining an immediate release layer comprising acetaminophen and pharmaceutically acceptable excipients with a sustained release layer made by wet granulating a sufficient amount of acetaminophen to comprise 68 to 94 percent of the total weight of the sustained relase layer with the Excipients of Part I and the Granulating Agent of Part II, drying and milling the resultant granulations, and then blending with the Excipients of Part III and compressing the two layers into a tablet, wherein the ingredients of Parts I, II and III comprise the following:

	Ingredient	Range of Parts by Weight of the Total Sustained Release Layer
Part I	Excipients	
	Hydroxyethyl Cellulose	5–25
	Microcrystalline Cellulose	5–25
Part II	Granulating Agent	
	Povidone	5–25
	Alcohol or Alcohol-Water	q.s.
Part III	Excipients	
	Pregelatinized Starch	2–15
	Microcrystalline Cellulose	5–45
	Magnesium Stearate	0–10
	Colloidal Silicon Dioxide	0–5

* * * * *

United States Patent [19]

Sparks et al.

[11] **Patent Number: 4,952,402**

[45] **Date of Patent: Aug. 28, 1990**

A2

[54] **CONTROLLED RELEASE POWDER AND PROCESS FOR ITS PREPARATION**

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[73] Assignee: **Elan Corporation, p.l.c.**, Athlone, Ireland

[21] Appl. No.: **169,447**

[22] Filed: **Mar. 17, 1988**

Related U.S. Application Data

[63] Continuation of Ser. No. 792,801, Oct. 30, 1985, abandoned.

[30] **Foreign Application Priority Data**

Oct. 30, 1984 [IE] Ireland 2788/84

[51] **Int. Cl.**[5] **A61K 9/58**; A61K 9/60; A61K 9/68; A61K 9/26

[52] **U.S. Cl.** **424/419**; 424/408; 424/417; 424/422; 424/423; 424/426; 424/427; 424/434; 424/437; 424/440; 424/441; 424/456; 424/462; 424/470; 424/494; 424/497

[58] **Field of Search** 424/484, 485, 486, 487, 424/488, 408, 417, 426, 427, 422, 423, 434, 437, 440, 441, 456, 462, 470, 494, 497

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Primary Examiner—Thurman K. Page
Attorney, Agent, or Firm—Robert Hardy Falk; Henry Croskell

[57] **ABSTRACT**

A controlled release powder containing discrete micro-particles for use in edible, pharmaceutical and other controlled release compositions is disclosed. The micro-particles have an average size in the range of from 0.1 to 125 μm. Each of the micro-particles is in the form of a micromatrix of an active ingredient uniformly distributed in at least one non-toxic polymer. The micro-particles have a predetermined release of active ingedient when the dissolution rate thereof is measured according to the Paddle Method of U.S. Pharmacopoeia XX at 37° C. and 75 r.p.m.

52 Claims, 15 Drawing Sheets

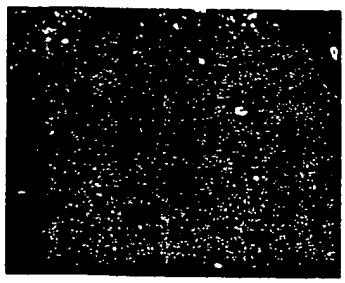

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FIG. 1.

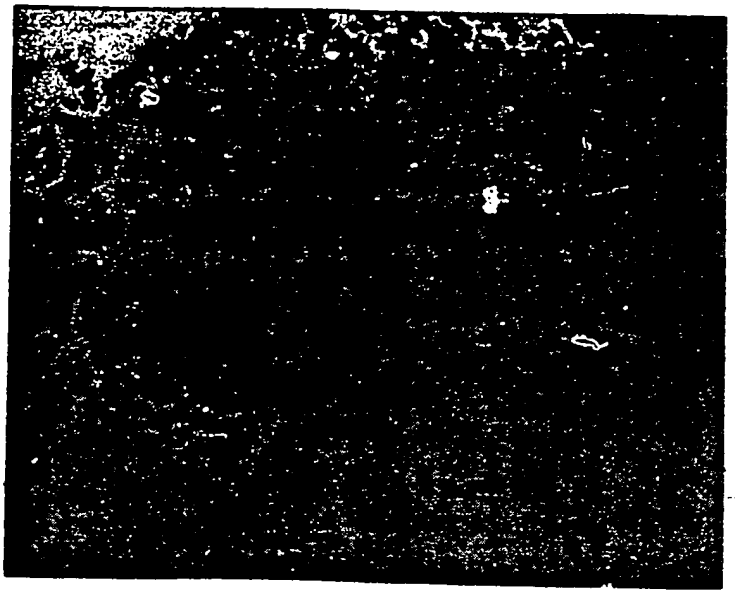
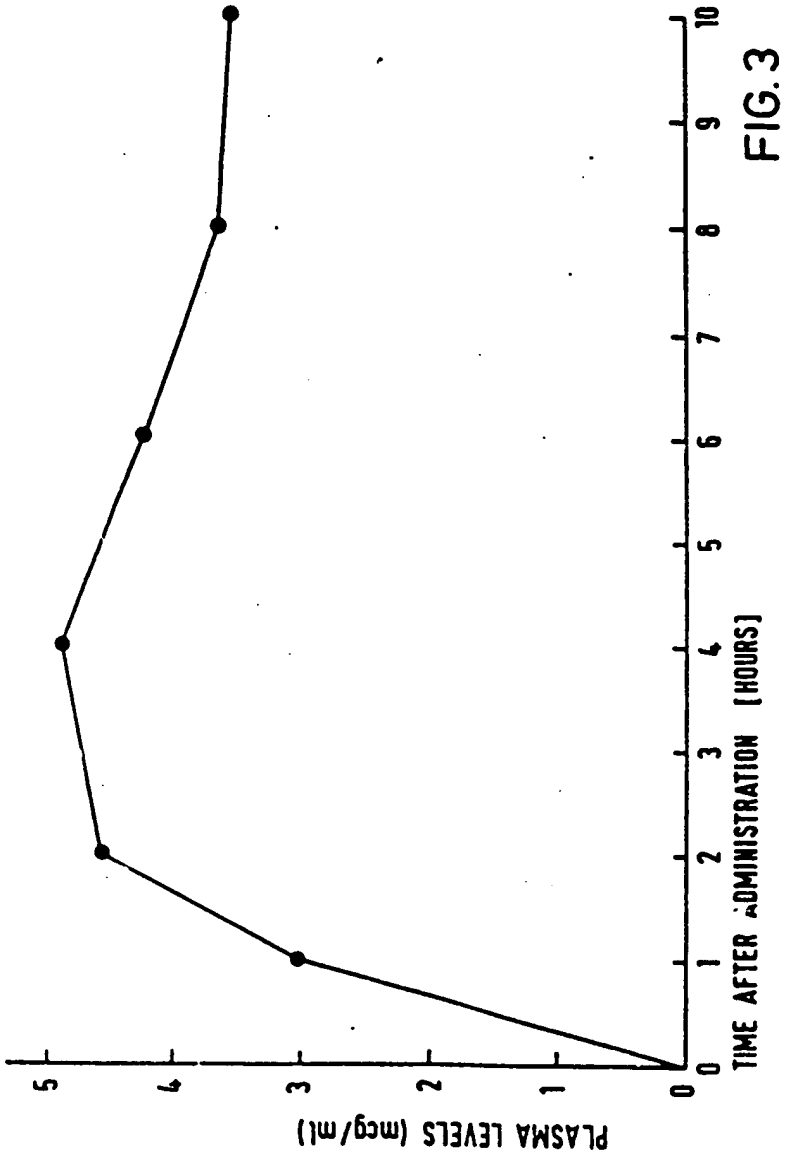


FIG. 2.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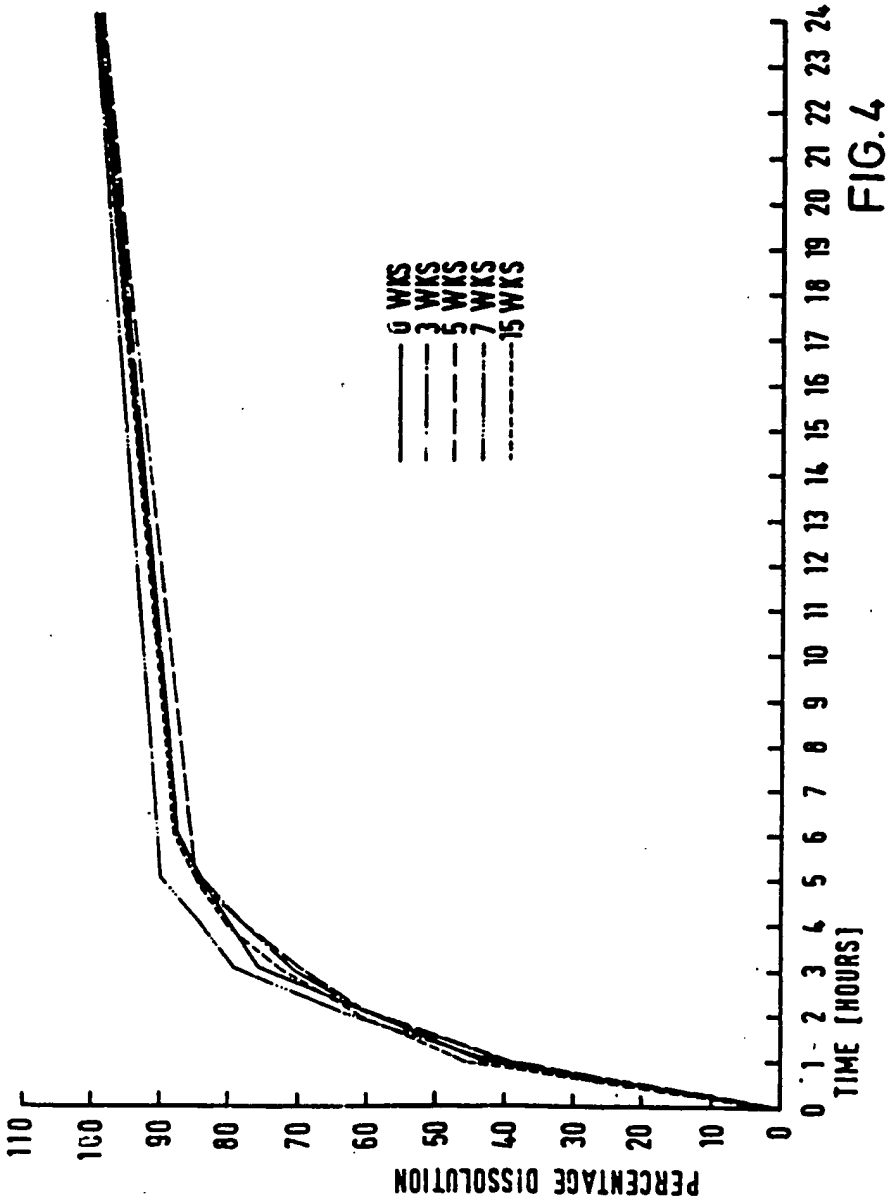
0
1
2
3
4
5
TIME AFTER ADMINISTRATION (HOURS)
0
1
2
3
4
5
6
7
8
9
10

FIG. 3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110
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
TIME [HOURS]
0 WKS
3 WKS
5 WKS
7 WKS
15 WKS

FIG. 4

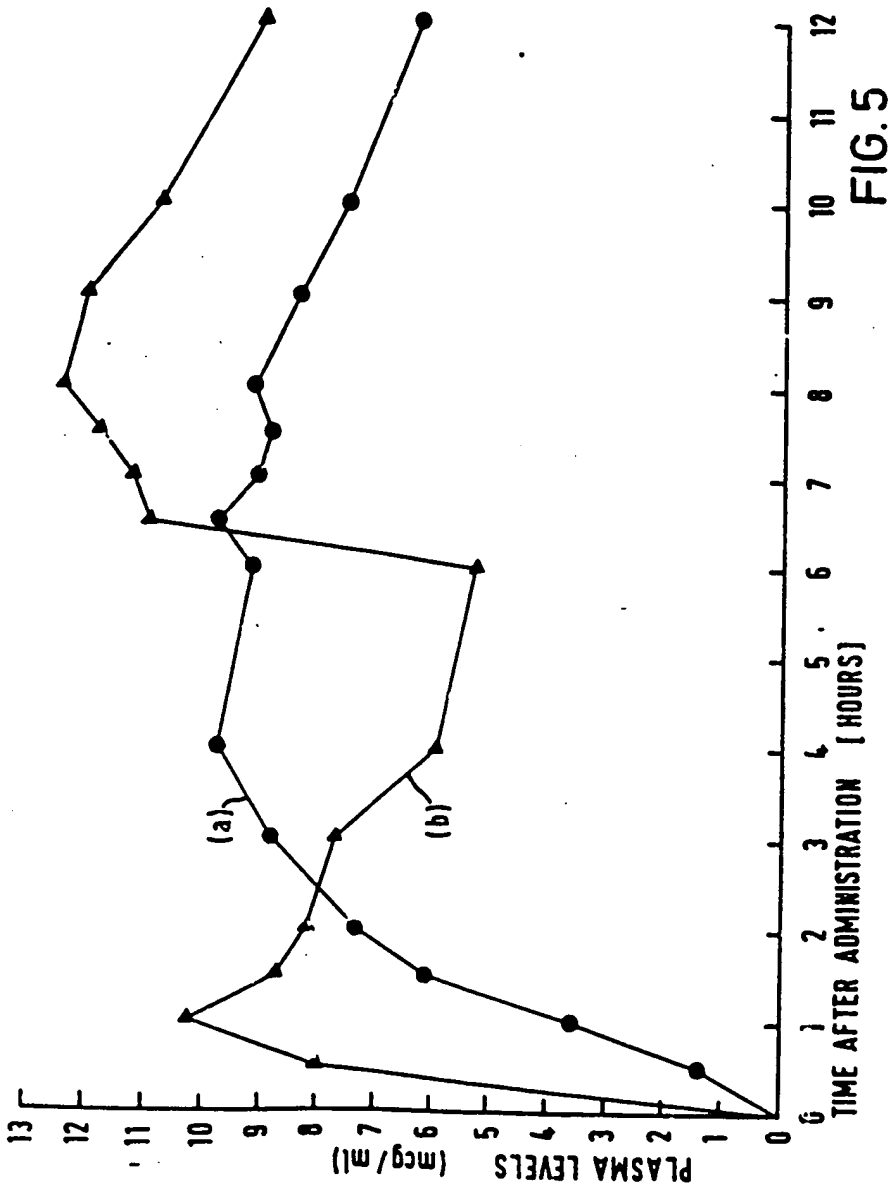

PLASMA LEVELS (mcg/ml)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
TIME AFTER ADMINISTRATION (HOURS)
0
1
2
3
4
5
6
7
8
9
10
11
12
(a)
(b)

FIG. 5

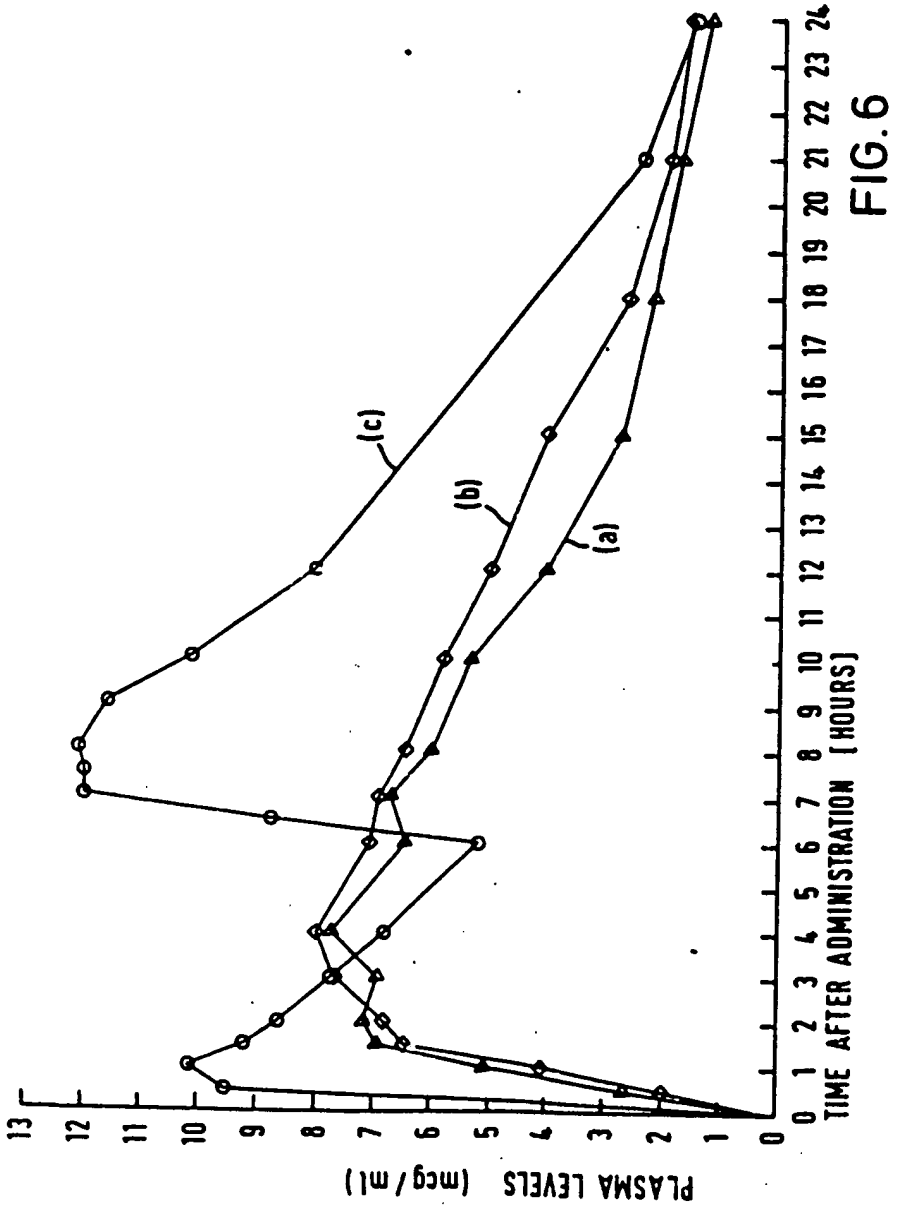
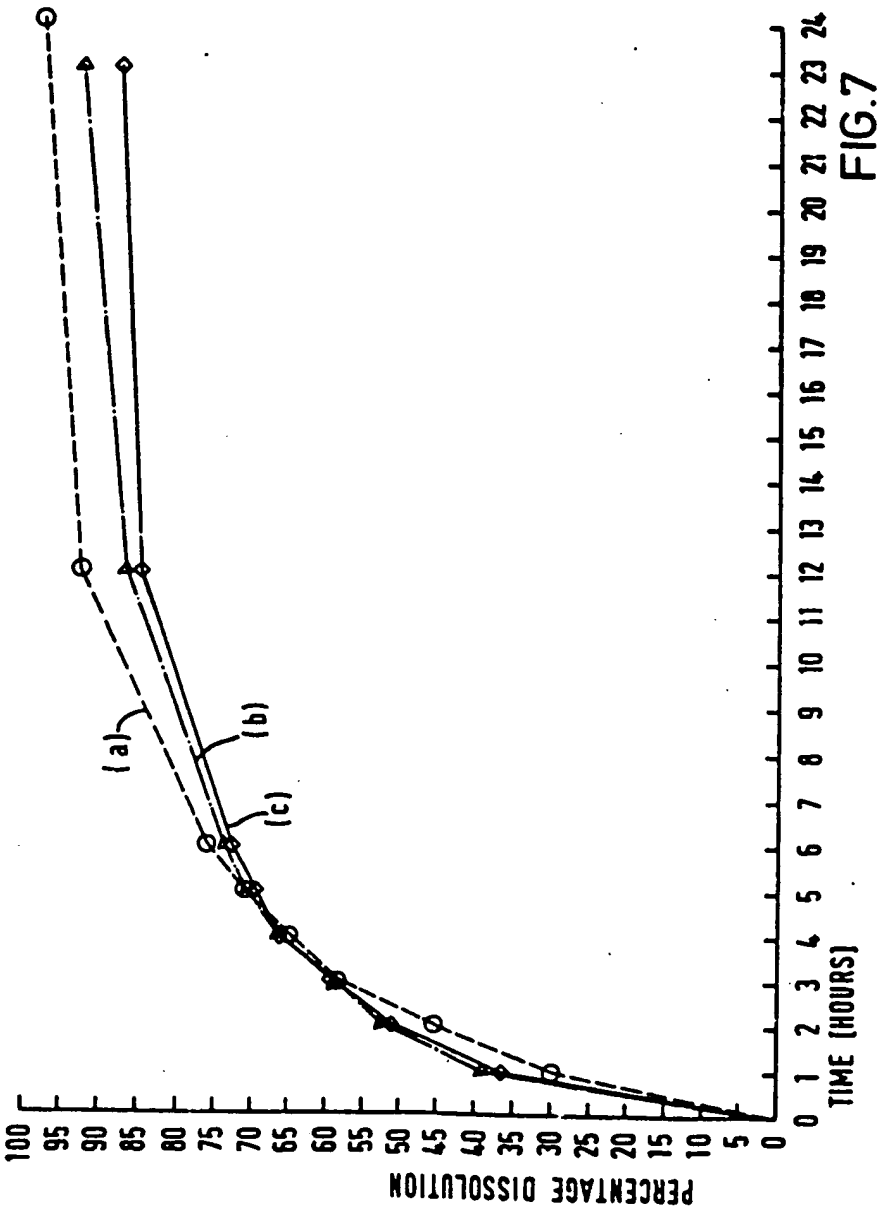

PLASMA LEVELS (mcg / ml)
0 1 2 3 4 5 6 7 8 9 10 11 12 13
TIME AFTER ADMINISTRATION (HOURS)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
(a)
(b)
(c)

FIG.6


PERCENTAGE DISSOLUTION
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TIME (HOURS)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
(a)
(b)
(c)

FIG.7

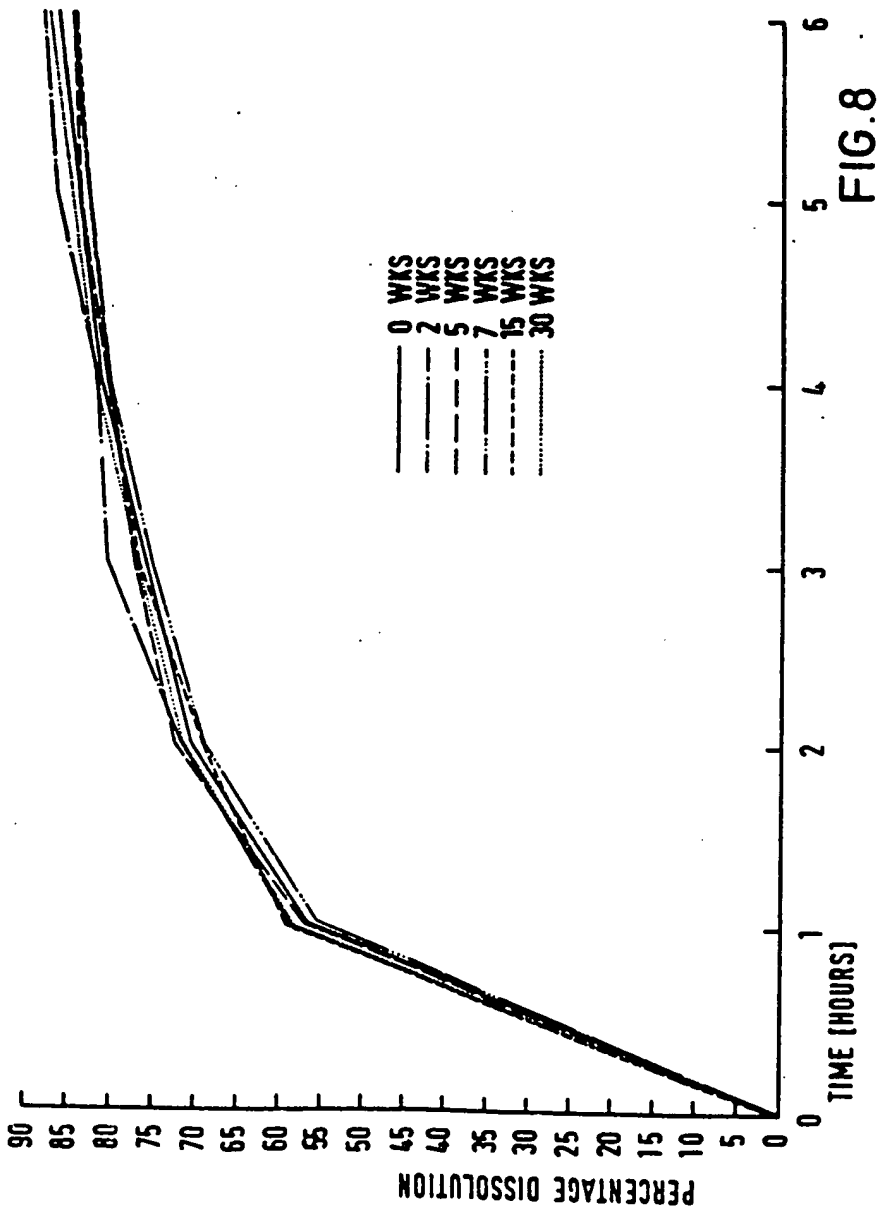
0 WKS
2 WKS
5 WKS
7 WKS
15 WKS
30 WKS
PERCENTAGE DISSOLUTION
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
0
1
2
3
4
5
6
TIME [HOURS]

FIG.8

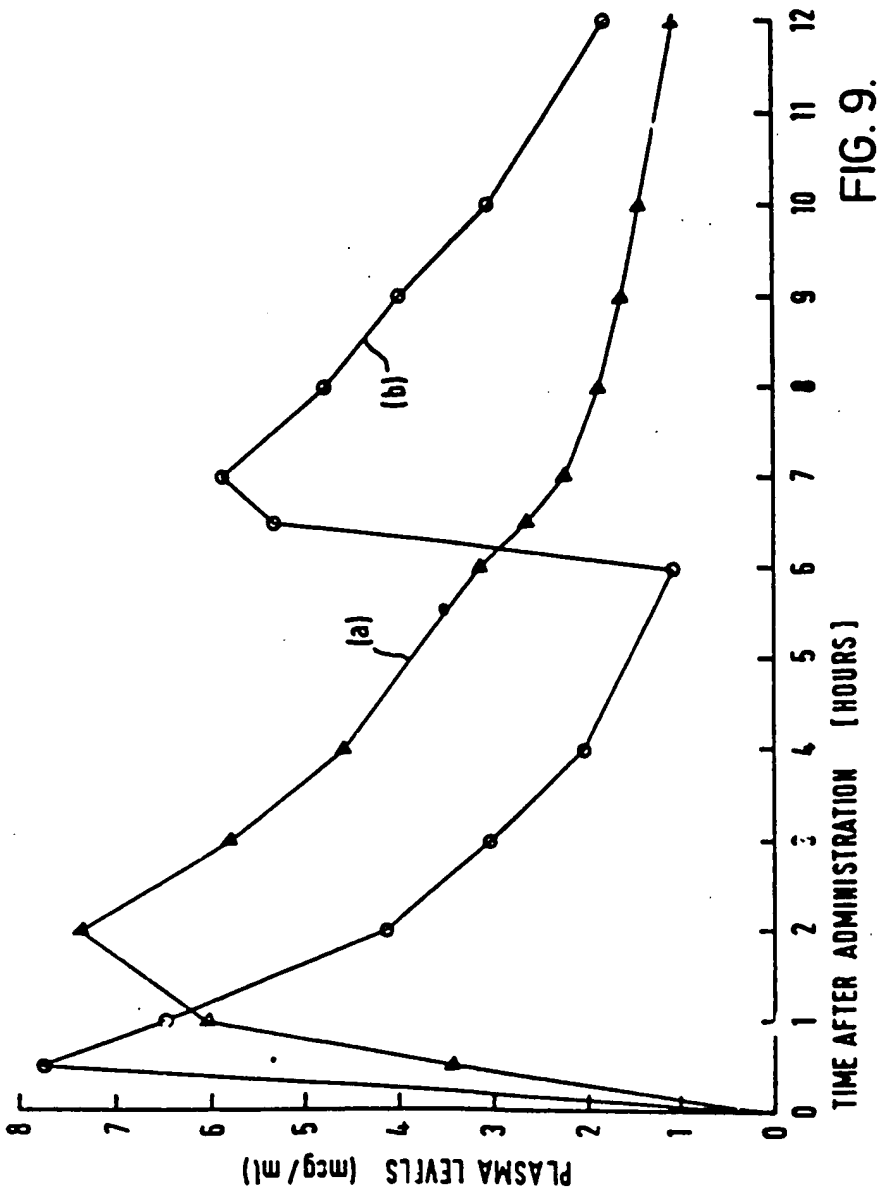
PLASMA LEVELS (mcg/ml)
0
1
2
3
4
5
6
7
8
TIME AFTER ADMINISTRATION (HOURS)
0
1
2
3
4
5
6
7
8
9
10
11
12
(a)
(b)

FIG. 9.

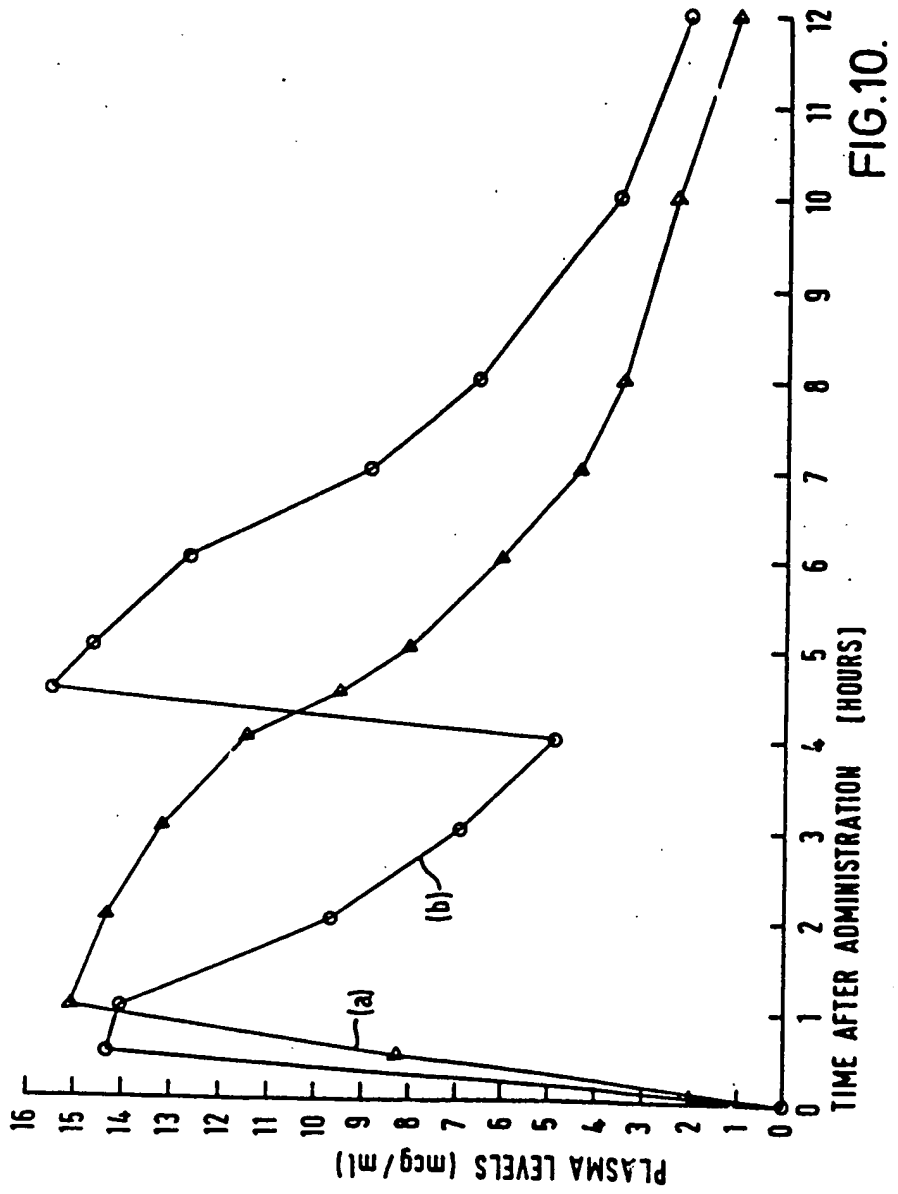
PLASMA LEVELS (mcg/ml)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
TIME AFTER ADMINISTRATION (HOURS)
0
1
2
3
4
5
6
7
8
9
10
11
12
(a)
(b)

FIG.10.

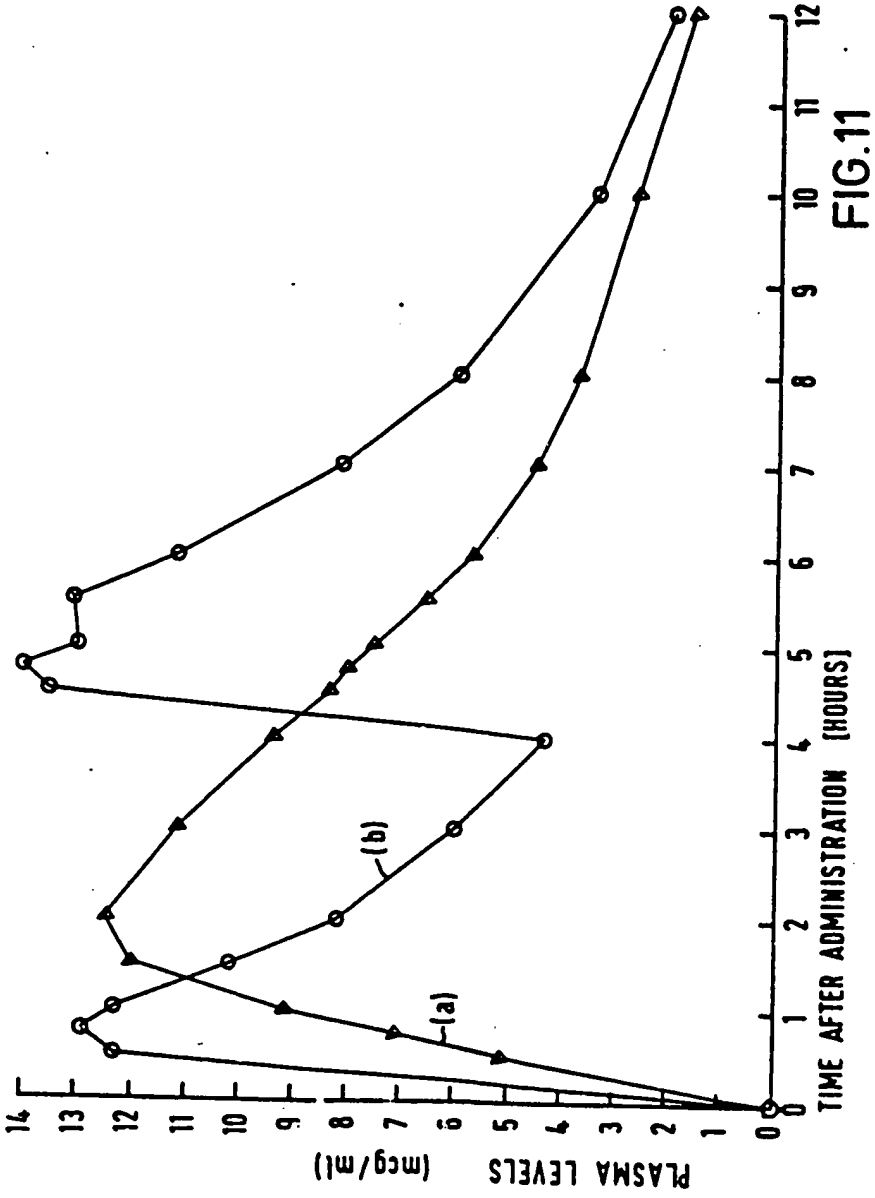
PLASMA LEVELS (mcg/ml)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
TIME AFTER ADMINISTRATION (HOURS)
0
1
2
3
4
5
6
7
8
9
10
11
12
(a)
(b)

FIG.11

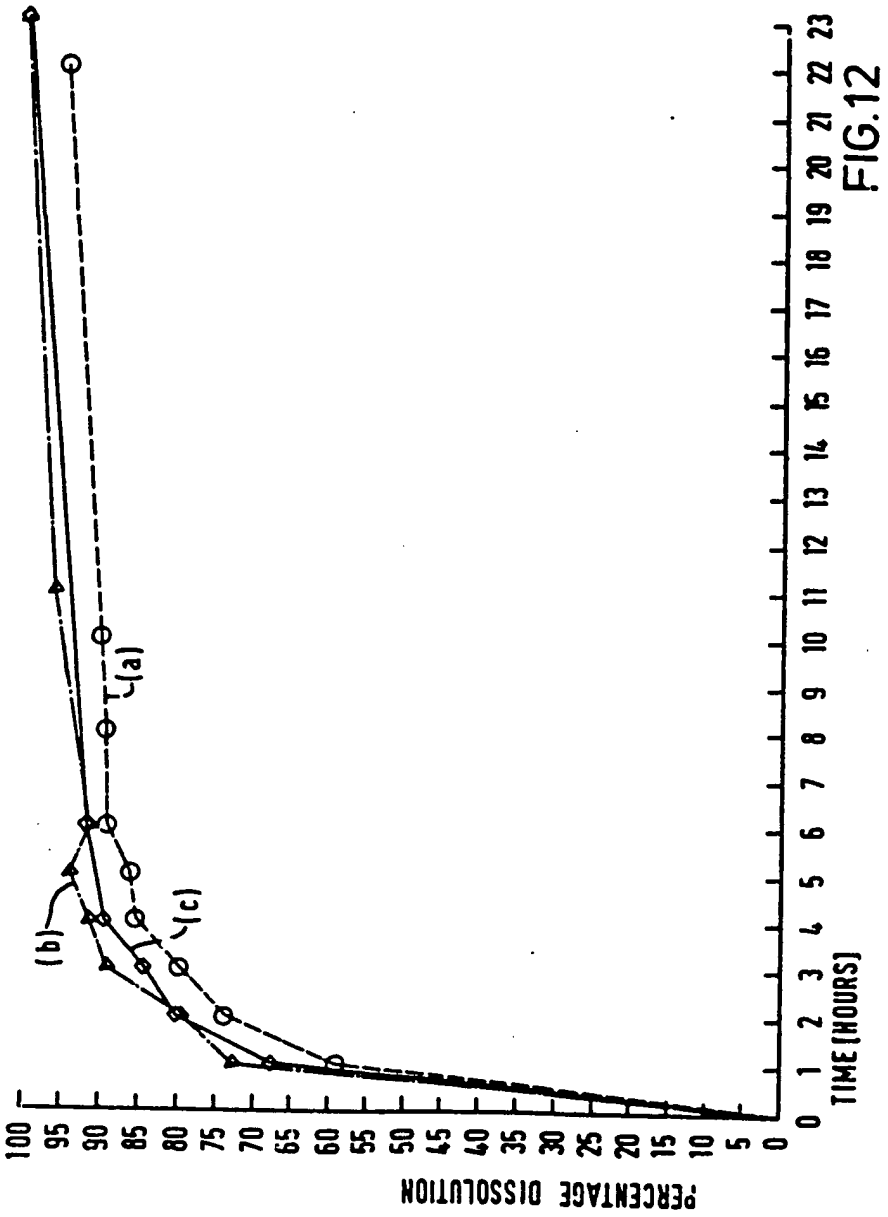
PERCENTAGE DISSOLUTION
100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
TIME (HOURS)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
(a)
(b)
(c)

FIG.12

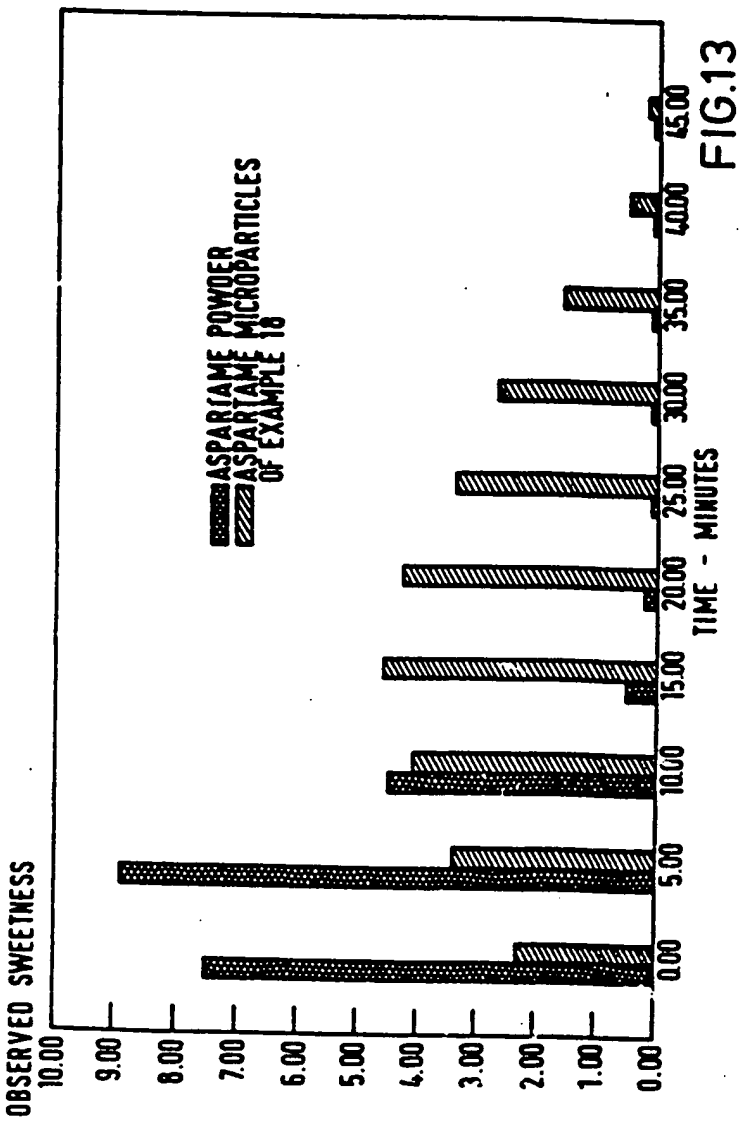
OBSERVED SWEETNESS
10.00
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
0.00
5.00
10.00
15.00
20.00
25.00
30.00
35.00
40.00
45.00
TIME - MINUTES
ASPARTAME POWDER
ASPARTAME MICROPARTICLES OF EXAMPLE 18

FIG.13

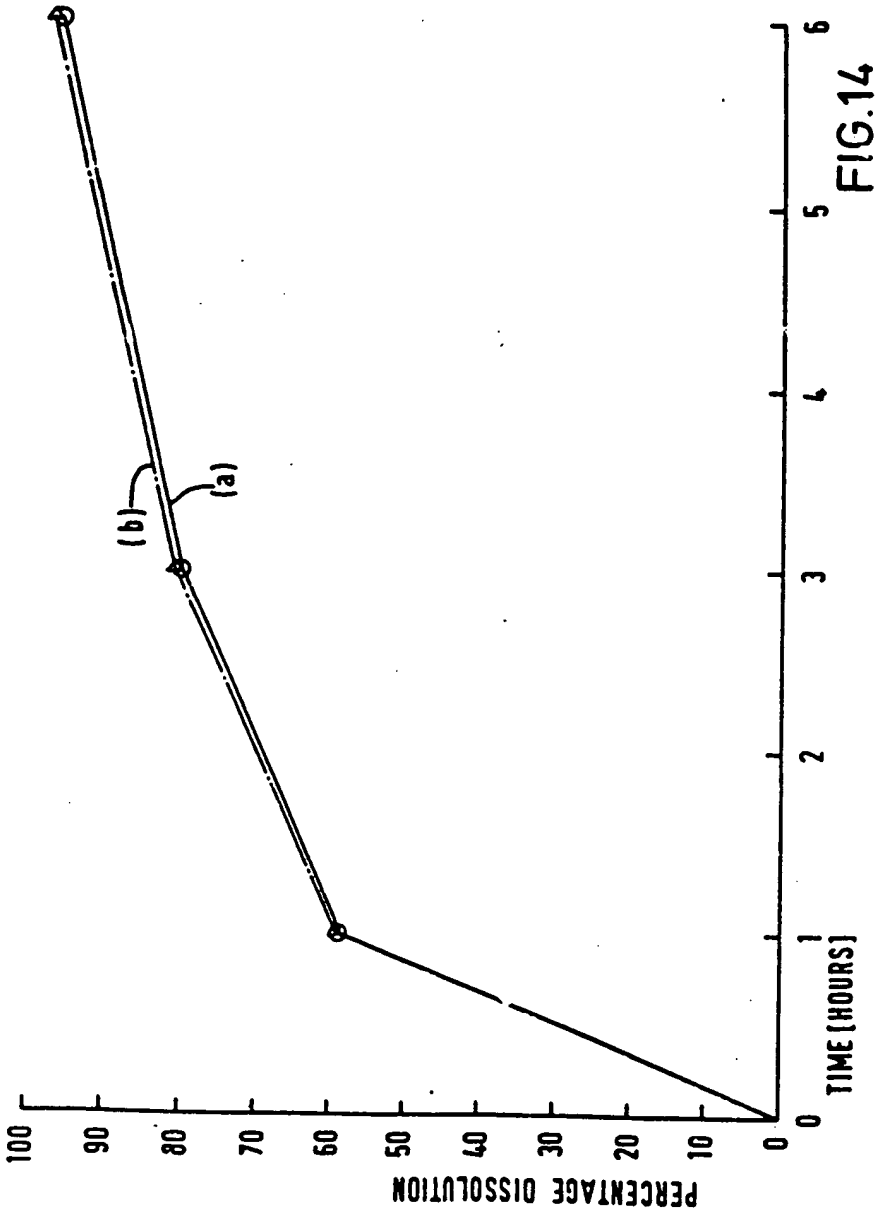
PERCENTAGE DISSOLUTION
100
90
80
70
60
50
40
30
20
10
0
TIME (HOURS)
0
1
2
3
4
5
6
(a)
(b)

FIG.14

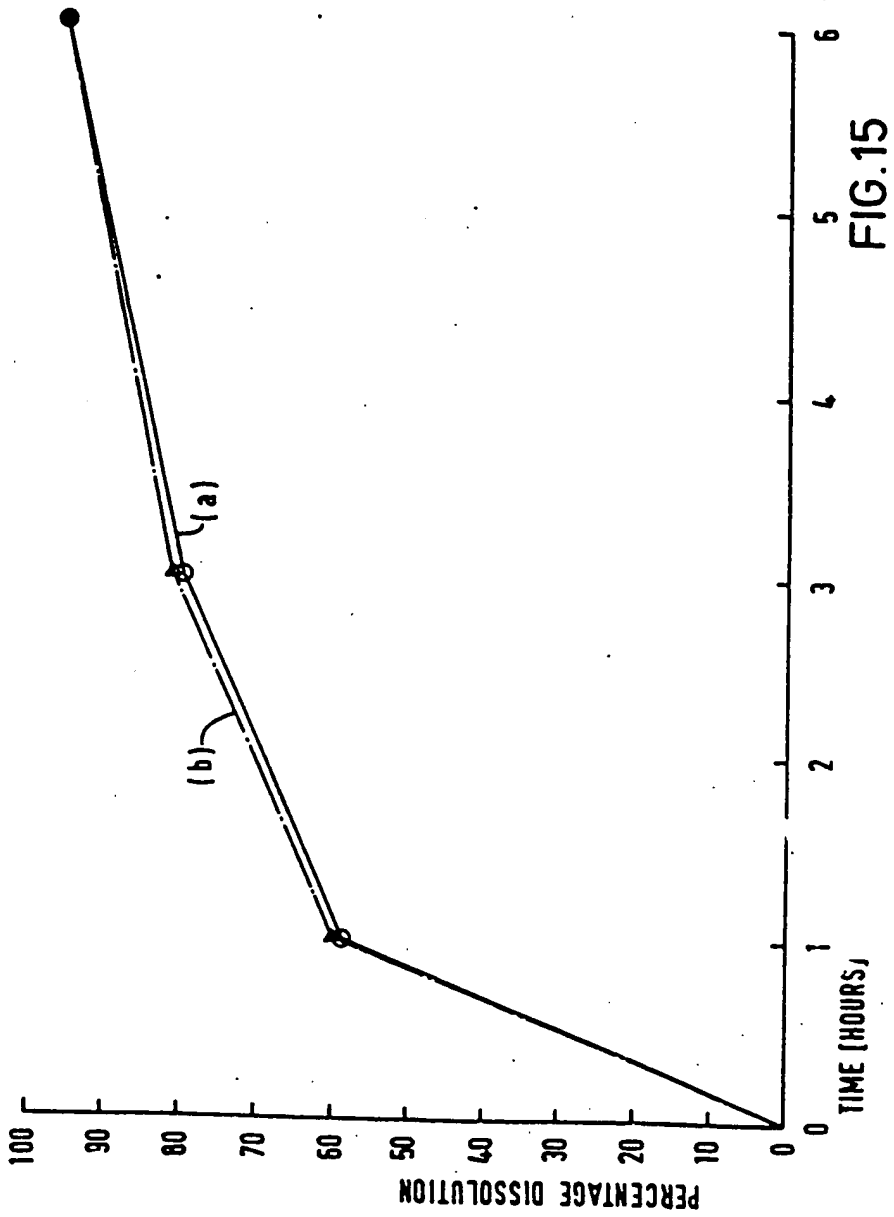
PERCENTAGE DISSOLUTION
100
90
80
70
60
50
40
30
20
10
0
TIME (HOURS)
0
1
2
3
4
5
6
(a)
(b)

FIG.15

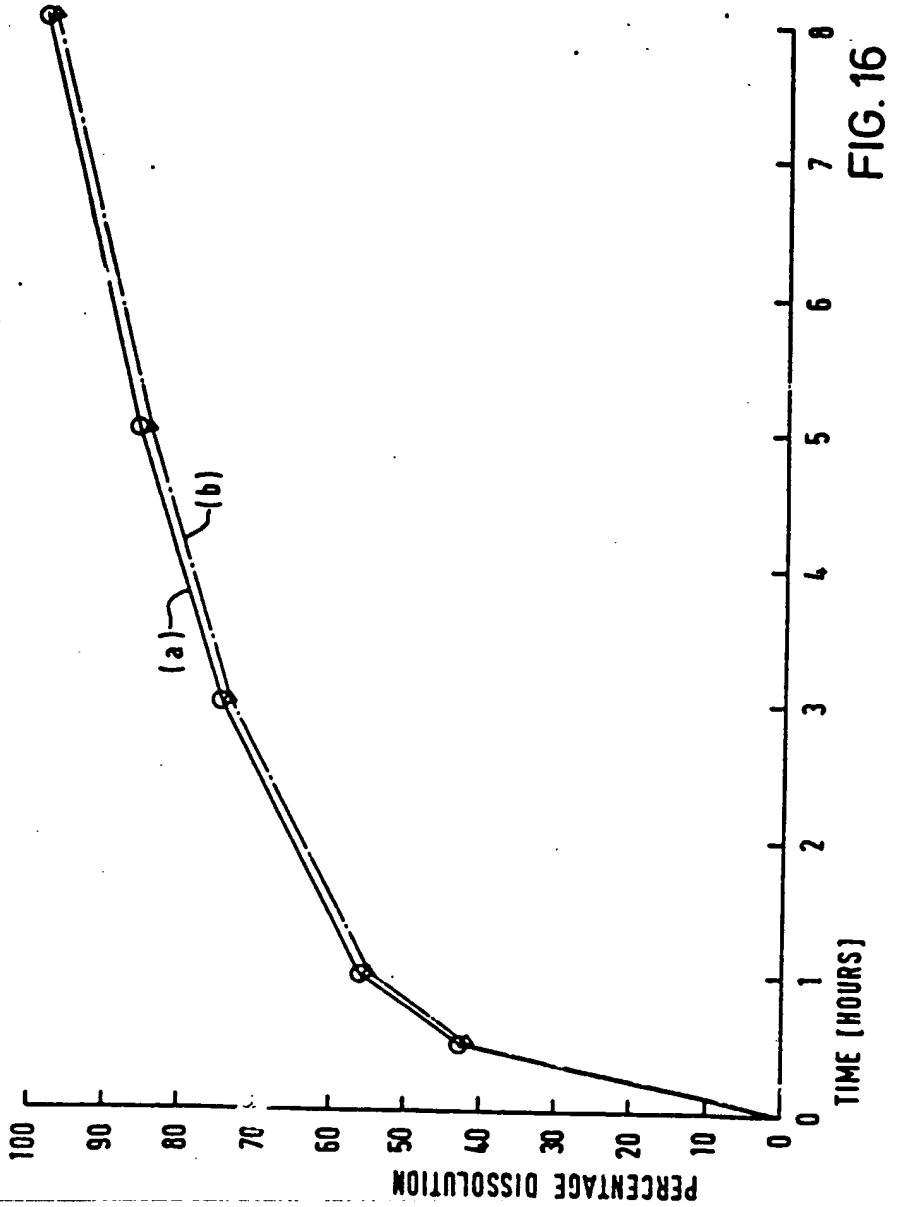
PERCENTAGE DISSOLUTION
100
90
80
70
60
50
40
30
20
10
0
TIME (HOURS)
0
1
2
3
4
5
6
7
8
(a)
(b)

FIG. 16

CONTROLLED RELEASE POWDER AND PROCESS FOR ITS PREPARATION

This application is a continuation of application Ser. No. 792,801, filed Oct. 30, 1985 abandoned.

BACKGROUND OF THE INVENTION

This invention relates to controlled release formulations and, in particular, to sustained release powders consisting of discrete micro-particles.

Many types of controlled or sustained release pellets are known which are loaded into capsules for oral administration. These pellets can be described as micro-particles and invariably have an average size greater than 400 μm.

Sustained release pellets cannot be readily formulated as liquids. Sustained release liquids are desirable for use as geriatric and pediatric formulations.

Various processes are known for the production of micro-spheres using solvent evaporation emulsion techniques. Known micro-encapsulation technique are generally employed for phase transformation, such as for the conversion of liquids to solids. Alternatively, such techniques may be used for protecting an active material, such as coating aspirin to mask its stomach irritant properties.

Sustained release liquids are known which contain ion exchange resins. In such sustained release liquids the active ingredient is bound to an ion exchange resin in the form of a reversible complex and is displaced therefrom in vivo. Such sustained release Lquids are described, for example, in French Patent Publication No. 2 278 325.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a controlled release powder of discrete micro-particles which can be readily formulated in liquid form but which can also be formulated in other sustained release forms such as tablets which have improved properties relative to the known forms.

It is another object of the present invention to provide a process for preparing the controlled release powder of the present invention. This process comprises:

(a) forming a solution of a polymer or polymers in a solvent;

(b) dissolving or dispersing an active ingredient in the polymer solution to form an uniform mixture; and

(c) removing the solvent from the mixture to obtain micro-particles having an average size of from 0.1 to 125 μm.

It is another object of the present invention to provide controlled release antibiotic formulations substantially free from the taste of the antibiotic for pharmaceutical or veterinary use. These controlled release antibiotic formulations are in the form of powders, non-aqueous suspensions of powders, or reconstitutable aqueous suspensions of powders according to the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

In describing the present invention, reference will be made to the accompanying drawings in which:

FIG. 1 is a half-tone drawing prepared from an electron micrograph of "pharmasomes" of the present invention containing theophylline;

FIG. 2 is a half-tone drawing prepared from an electron micrograph of "pharmasomes" of the present invention containing theophylline after theophylline has been leached out by dissolution in water for 24 hours;

FIG. 3 is a graph of plasma levels (mcg/ml) versus time after administration for a syrup containing "pharmasomes" containing theophylline;

FIG. 4 is a graph of percentage dissolution versus time for a suspension containing "pharmasomes" containing theophylline;

FIG. 5 is a comparison graph of plasma levels (mcg/ml) versus time after administration for a suspension containing "pharmasomes" containing theophylline and a conventional theophylline syrup;

FIG. 6 is a comparison graph of plasma levels (mcg/ml) versus time after administration for two suspensions containing different sized theophylline containing "pharmasomes" and a conventional theophylline syrup;

FIG. 7 is a graph of percentage dissolution versus time for three different suspensions containing theophylline containing "pharmasomes";

FIG. 8 is a graph of percentage dissolution versus time for a suspension containing acetaminophen containing "pharmasomes";

FIG. 9 is a comparison graph of plasma levels (mcg/ml) versus time after administration for a suspension containing acetaminophen containing "pharmasomes" and a conventional acetaminophen syrup;

FIG. 10 is a comparison graph of plasma levels (mcg/ml) versus time after administration for a suspension containing acetaminophen containing "pharmasomes" and a conventional acetaminophen syrup;

FIG. 11 is a comparison graph of plasma levels (mcg/ml) versus time after administration for a suspension containing acetaminophen containing "pharmasomes" and a conventional acetaminophen syrup;

FIG. 12 is a graph of percentage dissolution versus time for three different suspensions containing acetaminophen containing "pharmasomes";

FIG. 13 is a comparison graph of observed sweetness versus time for chewing gum containing aspartame containing "pharmasomes" and chewing gum containing aspartame powder;

FIG. 14 is a graph of percentage dissolution versus time for "pharmasomes" containing acetaminophen and for chewable tablets prepared therefrom;

FIG. 15 is a graph of percentage dissolution versus time for "pharmasomes" containing acetaminophen and for melt tablets prepared therefrom; and

FIG. 16 is a graph of percentage dissolution versus time for "pharmasomes" containing nifedipine and for capsules prepared therefrom.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides a controlled release powder containing discrete micro-particles for use in edible, pharmaceutical and other sustained release compositions. The powder of the present invention comprises particles containing an active ingredient and optionally an excipient in intimate admixture with at least one non-toxic polymer, each of the particles is in the form of a micromatrix with the active ingredient and the excipient, if present, uniformly distributed throughout the polymer. The particles have an average size of from 0.1 to 125 μm and have a predetermined release of active ingredient. The dissolution rate thereof can be

measured according to the Paddle Method of U.S. Pharmacopoeia XX at 37° C. and 75 r.p.m. Preferably, the particles have an average size of from 5 to 100 μm.

The term "pharmasomes" has been coined for the microparticles of the powder according to the present invention and this term is used hereinafter to refer to the micro-particles of the powder.

The controlled release powders according to the invention can permit a sustained release of active ingredient as hereinafter demonstrated.

The active ingredient, preferably, is a drug, a nutrient, a coloring agent, a fragrance, a herbicide, a pesticide, a flavoring agent or a sweetening agent.

The powder can be dispersed or suspended in a liquid vehicle and will maintain its sustained release characteristics for a useful period of time. These dispersions or suspensions have both chemical stability and stability in terms of dissolution rate.

The polymer may be soluble, insoluble, permeable, impermeable or biodegradable. The polymers may be polymers or copolymers. The polymer may be a natural or synthetic polymer. Natural polymers include polypeptides, polysaccharides and alginic acid. A suitable polypeptide is zein and a suitable polysaccharide is cellulose.

Representative synthetic polymers include alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro cellulo s, polymers of acrylic and methacryli. acids and esters thereof, polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes and polyurethanes and co-polymers thereof. The polymer to be used is governed by its toxicity and its compatibility with the particular active ingredient being used and can be selected without difficulty by those skilled in the art.

Particularly suitable polymers include: methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight) cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxymethyl cellulose, cellulose triacetate, cellulose sulphate sodium salt, poly(methyl methacrylate) poly(ethyl methacrylate), poly(butylmethacrylate), poly(isobutyl methacrylate), poly(hexylmethacrylate), poly(isodecyl methacrylate) poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), poly(ethylene), poly(ethylene) low density, poly(ethylene) high density, poly(propylene), poly(ethylene glycol), poly(ethylene oxide), poly(ethylene terephthalate), poly(vinyl alcohol), poly(vinyl isobutyl ether), poly(vinyl acetate), poly(vinyl chloride) and polyvinylpyrrolidone.

Especially suitable co-polymers include: butyl methacrylate/isobutyl methacrylate co-polymer, high molecular weight, methylvinyl ether/maleic acid co-polymer, methylvinyl ether/maleic acid, monoethyl ester co-polymer, methylvinyl ether/maleic anhydride co-polymer and vinyl alcohol/vinyl acetate co-polymer.

Representative biodegradable polymers include, polylactides, polyglycolides, poly(ethylene terephthalate) and polyurethane.

Representative acrylates and methacrylates are polyacrylic and methacrylic polymers such as those sold under the Trade Mark Eudragit.

When the active ingredient is a drug there is essentially no limitation on the type of drug which may be used.

Representative active ingredients include antacids, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, anti-infectives, psychotropics, anti-manics, stimulants, anti-histamines, laxatives, decongestants, vitamins, gastro-intestinal sedatives, anti-diarrheal preparations, anti-anginal drugs, vasodilators, anti-arrhythmics, anti-hypertensive drugs, vasoconstrictors and migraine treatments, anti-coagulants and anti-thrombotic drugs, analgesics, anti-pyretics, hypnotics, sedatives, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypoglycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, mineral and nutritional additives, anti-obesity drugs, anabolic drugs, erythropoietic drugs, anti-asthmatics, bronchodilators, expectorants, cough suppressants, mucolytics and anti-uricemic drugs.

Typical active ingredients include gastro-intestinal sedatives such as metoclopramide and propantheline bromide; antacids such as aluminium trisilicate, aluminium hydroxide and cimetidine; anti-inflammatory drugs such as phenylbutazone, indomethacin, naproxen, ibuprofen, flurbiprofen, diclofenac, dexamethasone, prednisone and prednisolone; coronary vasodilator drugs such as glyceryl trinitrate, isosorbide dinitrate and pentaerythritol tetranitrate; peripheral and cerebral vasodilators such as soloctidilum, vincamine, naftidrofuryl oxalate, co-dergocrine mesylate, cyclandelate, papaverine and nicotinic acid; anti-infective substances such as erythromycin stearate, cephalexin, nalidixic acid, tetracycline hydrochloride, ampicillin, flucloxacillin sodium, hexamine mandelate and hexamine hippurate; neuroleptic drugs such as flurazepam, diazepam, temazepam, amitryptyline, doxepin, lithium carbonate, lithium sulfate, chlorpromazine, thioridazine, trifluperazine, fluphenazine, piperothiazine, haloperidol, maprotiline hydrochloride, imipramine and desmethylimipramine; central nervous stimulants such as methylphenidate, ephedrine, epinephrine, isoproterenol, amphetamine sulfate and amphetamine hydrochloride; antihistamic drugs such as diphenhydramine, diphenylpyraline, chlorpheniramine and brompheniramine; anti-diarrheal drugs such as bisacodyl and magnesium hydroxide; the laxative drug, dioctyl sodium sulfosuccinate; nutritional supplements such as ascorbic acid, alpha tocopherol, thiamine and pyridoxine; anti-spasmodic drugs such as dicyclomine and diphenoxylate; drugs affecting the rhythm of the heart such as verapamil, nifedipine, diltiazem, procainamide, disopyramide, bretylium tosylate, quinidine sulfate and quinidine gluconate; drugs used in the treatment of hypertension such as propranolol hydrochloride, guanethidine monosulphate, methyldcpa, oxprenolol hydrochloride, captopril and hydralazine; drugs used in the treatment of migraine such as ergotamine; drugs affecting coagulability of blood such as epsilon aminocaproic acid and protamine sulfate; analgesic drugs such as acetylsalicylic acid, acetaminophen, codeine phosphate, codeine sulfate, oxycodone, dihydrocodeine tartrate, oxycodeinone, morphine, heroin, nalbuphine, butorphanol tartrate, pentazocine hydrochloride, cyclazacine, pethidine, buprenorphine, scopolamine and mefenamic acid;

anti-epileptic drugs such as phenytoin sodium and sodium valproate; neuromuscular drugs such as dantrolene sodium; substances used in the treatment of diabetes such as tolbutamide, diabenese glucagon and insulin; drugs used in the treatment of thyroid gland disfunction such as triiodothyronine, thyroxine and propylthiouracil, diuretic drugs such as furosemide, chlorthalidone, hydrochlorthiazide, spironolactone and triamterene; the uterine relaxant drug ritodrine; appetite suppressants such as fenfluramine hydrochloride, phentermine and diethylpropion hydrochloride; anti-asthmatic and bronchodilator drugs such as aminophylline, theophylline, salbutamol, orciprenaline sulphate and terbutaline sulphate; expectorant drugs such as guaiphenesin; cough suppressants such as dextromethorphan and noscapine; mucolytic drugs such as carbocisteine; anti-septics such as cetylpyridinium chloride, tyrothricin and chlorhexidine; decongestant drugs such as phenylpropanolamine and pseudoephedrine; hypnotic drugs such as dichloralphenazone and nitrazepam; anti-nauseant drugs such as promethazine theoclate; haemopoietic drugs such as ferrous sulphate, folic acid and calcium gluconate; uricosuric drugs such as sulphinpyrazone, allopurinol and probenecid.

Particularly preferred active ingredients are: ibuprofen, acetaminophen, 5-amino-salicyclic acid, dextromethorphan, propranolol, theophylline, diltiazem, methyldopa, pseudoephedrine, cimetidine, cephalexin, cephaclor, cephradine, naproxen, piroxican, diazepam, diclofenac, indomethacin, amoxycillin, pivampicillin, becampicillin, dicloxacillin, erythromycin, erythromycin stearate lincomycin, co-dergocrine mesylate, doxycycline, dipyridamole, frusemide, triamterene, sulindac, nifedipine, atenolol, lorazepam, glibenclamide, salbutamol, trimethoprim/sulphamethoxazole, spironolactone, carbinoxamine maleate, guaiphenesin, potassium chloride and metoprolol tartrate.

Especially preferred active ingredients include theophylline, acetaminophen and potassium chloride.

The active ingredient may also be a saccharin for use in edible compositions wherein it is desired to obtain a controlled release of saccharin, such as, for example in chewing gums. The active ingredient may also be other sweetening agents, such as, for example, aspartame which is especially suitable for use in chewing gums.

The present invention also provides a process for preparing the controlled release powder according to the invention which comprises:

(a) forming a solution of the polymer or polymers in a solvent;

(b) dissolving or dispersing the active ingredient in said polymer solution to form an uniform mixture; and

(c) removing the solvent from the mixture to obtain micro-particles having an average size of from 0.1 to 125 μm.

The particles obtained, preferably, have an average size of from 5 to 100 μm.

The solvent is selected from water, alcohols, ketones, halogenated aliphatic compounds, halogenated aromatic hydrocarbon compounds, aromatic hydrocarbon compounds and cyclic ethers or a mixture thereof.

Especially preferred solvents include, water, hexane, heptane, methanol, ethanol, acetone, methylethyl ketone, methylisobutyl ketone, methylene chloride, chloroform, carbon tetrachloride, toluene, xylene and tetrahydrofuran.

The choice of solvent of solvents will be dictated by the particular polymer or polymers selected and can be chosen without difficulty by those skilled in the art. For example, suitable solvents for use with the celluloses are acetone or a mixture of methanol and methylene chloride.

The concentration of the polymer in the solvent will normally be less than 75% by weight. Normally the concentration will be in the range of 10-30% by weight.

If the active ingredient is not soluble in the polymer solution the particle size of the active ingredient is reduced to less than 10 μm. The reduction of particle size may be achieved by milling, for example, by ball milling or jet milling.

The active ingredient may, of course, be a liquid.

The ratio of drug to polymer will vary within wide limits, such as within the range of from 0.1:10 to 10:1.

The uniform mixture of the active ingredient in the polymer solution may be achieved by rapid and continuous mixing.

The removal of the solvent and the formation of particles of the desired size may be achieved in a number of ways as described below.

Spray Drying

The mixture of active ingredient and polymer in the solvent is sprayed into a stream of hot air in a conventional manner. This causes the solvent to evaporate and the powder is collected in the spray drying vessel.

The size of the particles may be controlled in a number of ways, for example, by pre-selecting the inlet and outlet temperature of the spray drying vessel; the rate of introduction of the spray, the size of the spray tip or the ratio of the concentration of active ingredient to polymer.

2. USE OF AN EXTERNAL LIQUID PHASE

The mixture of active ingredient and polymer, which is in the form of a solution or suspension, is poured into a liquid external phase. The liquid external phase comprises a solvent which is immiscible or partially immiscible with the active ingredient/polymer mixture.

The choice of external liquid phase will be determined by the particular combination of active ingredient and polymer selected. Suitable liquids for the external liquid phase include water, aqueous solutions, for example, sugar solutions, organic solvents, mineral oil, vegetable oils, fixed oils, syrups or silicones. The aqueous solution may include a thickening agent, such as xanthan gum, to increase the viscosity thereof. Oils may be made more viscous by the addition of substances such as magnesium stearate. The external liquid phase may also comprise a solution of a different pH, for example, a buffer.

The ratio of external liquid phase to polymer mixture will be at least 2:1.

Following addition of the active ingredient/polymer mixture to the external liquid phase, the two phase mixture obtained is emulsified, for example, by rapid mixing. The emulsion formed may be either stable or unstable. Globules of the active ingredient/polymer are thereby formed in the emulsion.

The solvent may be removed in a number of ways. If the solvent is volatile it can be removed passively. For example if the solvent is acetone it would normally be removed by evaporation during the mixing step. The particles formed are then harvested by filtration of centrifugation.

The solvent can also be removed by heating while mixing the two phase mixture. For example, the solvent may also be removed on a rotary film evaporator. The solvent may also be removed under vacuum with or without heating. Microwave drying may also be employed with or without the application of a vacuum. Another mode of solvent removal is freeze drying.

After harvesting of the micro-particles, they will normally be given successive washings with a suitable solvent, followed by drying. For example, when the solvent used is acetone and the external liquid phase is mineral oil, the microparticles will be successively washed with hexane and then dried at 45° C.

On a commercial scale emulsification of the mixture may be achieved by emulsification with an in-line mixer or mixers.

The particle size may be controlled in a number of ways. For example, the particle size may be controlled by the rate of mixing, the viscosity of the external liquid phase, the viscosity of the internal phase, the active ingredient particle size or the volatility of the solvent.

3. Other methods for the removal of the solvent include phase separation, interfacial polymer deposition and coacervation.

The optional excipient used in association with the active ingredient will frequently have an active role to play following administration. For example, the excipient may be a surface-active agent which facilitates the transport of water into the particles, for example, sodium lauryl sulphate or a polyoxyethylene sorbitan ester such as that sold under the Trade Mark Tween a product of ICI America, Atlas Division. The excipient may also be an active transport such as, for example, glucose or one or more amino acids.

The excipient may comprise one or more organic acids which facilitate the dissolution of drugs which are poorly soluble in alkaline media. Such acids include, for example, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid and tartaric acid. Similarly, the excipient may comprise one or more basic materials which facilitate the dissolution of drugs which are poorly soluble in acid media. Such basic materials include sodium carbonate, sodium citrate and sodium bicarbonate.

When the active ingredient is a drug, the micro-particles according to the invention may be formulated in a wide variety of forms. Pharmaceutical formulations according to the invention include pills and tablets, for example, coated tablets, effervescent tablets, chewable tablets, molded tablets and melt tablets. The particles according to the invention may be compressed into tablets and optionally coated without any substantial change occurring in the particles. Furthermore, because of the micro-particulate nature of the particles they are unlikely to be significantly degraded or ground by any chewing action.

Power formulations according to the invention include dusting powder and douche powders.

The particles according to the invention may also be loaded into capsules which may be either soft gelatin capsules or hard gelatin capsules.

Other solid dosage forms include pessaries, rectal suppositories, vaginal tablets and vaginal inserts.

The particles according to the invention may also be used in implants and ocular inserts.

The powders can also be formulated in forms suitable for topical application, such as, for example, creams or ointments and for transdermal delivery, for example, in the form of transdermal patches.

The micro-particulate powders according to the invention may also be used in the form of foams, gels, pastes, gums, mucilages and jellies.

Other suitable formulations incorporating the micro-particles according to the invention include inhalants, magmas, intrauterine devices, patches, biodegradable wound dressings and other topical dressings.

The micro-particulate powders according to the invention are especially suitable for formulation as liquids for oral, local or parenteral administration. Thus, they can be formulated in liquid form for use as eye drops, nasal drops, ear drops, suspensions, syrups, infusion and injectable solutions. The powders can also be formulated as nasal sprays. The injectable solutions include intravenous, subcutaneous and intramuscular injectable solutions.

The oral suspensions and syrups according to the invention are particularly suitable for use in geriatric and pediatric medicine. The liquids formed have good mouth feel. Furthermore, because the polymer substantially coats the active ingredient, the coating masks any unpleasant taste.

A characteristic of good mouth feel also applies to chewable and effervescent tablets. Because of the micro-particulate nature of the powder one does not experience a granular sensation.

Preferred pediatric liquids according to the invention are suspensions or syrups of bronchial relaxants, analgesics, anti-pyretics, anti-tussives, anti-spasmodics, anti-nauseants, anti-histamines, anti-epileptics and antibiotics.

Other especially suitable liquid formulations according to the invention are non-aqueous suspensions of highly water soluble or water insoluble active ingredients. Suitable drugs for these formulations include dextromethorphan, guaiphenesin and pseudoephedrine or a salt thereof or potassium chloride.

The liquid formulations have good shelf life and demonstrate chemical stability and stability in terms of dissolution rate for up to six months. It is estimated that the shelf life can be as long as five years.

In the liquid formulations according to the invention a concentration of active ingredient of up to 1 g per 5 ml can be achieved.

Heretofore many drugs have not been stable in liquid form, for example, analgesics, necessitating a dosage regimen of every 4–6 hours. The liquids according to the invention offer versatility and the possibility of twice daily administration for a medicament such as, for example, analgesics, anti-histamines and bronchial relaxants.

The taste masking feature of the powders according to the invention is of significant importance in the area of pediatric medicine. However, this feature is of equal importance in veterinary medicine. For example, in the case of antibiotics such as erythromycin which have an extremely unpleasant bitter taste it is virtually impossible to administer such antibiotics orally to animals because it is not possible to successfully mask the bitter taste. Accordingly, such known oral formulations are rejected by animals.

The present invention therefore in one important aspect provides controlled release antibiotic formulations substantially free from the taste of said antibiotic for pharmaceutical or veterinary use which:

(a) are in the form of powders according to the invention;

(b) are in the form of non-aqueous suspensions of the powders according to the invention; or

(c) are in the form of reconstitutable aqueous suspensions of the powders according to the invention.

The powders according to the invention can be used in pre-mixes for animal feedstuffs and other feed additives.

In addition to drugs, nutritional supplements such as vitamins can be administered orally to animals using the powders according to the invention.

Suitable veterinary preparations according to the invention include veterinary feeds, boluses, drenches and washes.

In the agricultural field the powders according to the invention can also be used for preparation of controlled release herbicides and pesticides.

In the cosmetics field one use of the controlled release powders according to the invention is as sustained release fragrance particles for use in talcum powders, creams, lotions and other cosmetic preparations.

Each of the particles of the controlled release powder according to the invention represents a true micromatrix with the active ingredient and optionally one or more excipients uniformly distributed therethrough as depicted in FIG. 1 of the accompanying drawings which is a half-tone drawing prepared from an electron micrograph of "pharmasomes" containing theophylline and prepared as described in Example 1 below. The theophylline can be observed to form veins or a labyrinth throughout the polymeric material of the "pharmasomes". FIG. 2 is a half-tone drawing prepared from an electron micrograph of the "pharmasomes" after the theophylline has been leached out by dissolution in water for 24 hours. It may be observed that a matrix structure of polymeric materials remains.

The micromatrix nature of the particles can also be demonstrated by their dissolution profile. Referring, for example, to Examples 1 and 2 hereinbelow, it is found that the dissolution rate (D) is directly proportional to the square root of time (t), after an initial burst of release of active ingredient, according to the following equation:

$$D \sim \sqrt{t}$$

The initial burst of release of active ingredient is considered to be active ingredient lying close to the surface of the particles. The dissolution rate is dependent on the amount of active ingredient remaining in the particle matrix at any given time. Theoretically the last molecule of active ingredient never leaches out. The dissolution rate is assumed to reach 100% at infinity.

The particles according to the invention also have a degree of porosity which can be calculated from the absolute density of the particles measured on a pycnometer. The dissolution rate of the particles according to the invention is also found to relate to the degree of porosity of said particles.

The microparticles according to the invention are to be distinguished from microcapsules in that in the latter the active ingredient is encapsulated by a polymer coating, whereas in the former the active ingredient is uniformly distributed throughout the polymeric material as described above and as illustrated in FIGS. 1 and 2 of the accompanying drawings.

The invention will now be further illustrated by the following examples. The following examples are intended to be merely illustrative of the present invention and are not intended to be limiting in any way. In the following examples the dissolution rate of the various pharmaceutical formulations is measured by the Paddle Method of U.S. Pharmacopoeia XX at 37° C. and 75 r.p.m., using 200 mg of sample per 900 ml of simulated intestinal fluid excluding enzymes.

EXAMPLE 1

Preparation of micro-particles containing theophylline

Theophylline was ground in a motorized ball mill and then sieved through a 38 μm mesh sieve.

Cellulose acetate butyrate (CAB) was dissolved in acetone to give a concentration of CAB in acetone of 15% w/v.

Hexane (20 ml) was added to an aliquot of the CAB solution (100 g) with constant stirring.

A portion of the sieved theophylline (10 g) was then added to the polymer solution under constant agitation to ensure at an even dispersion of the theophylline. This product constituted an internal phase for the subsequent emulsification step.

Magnesium stearate was dissolved in heavy mineral oil U.S. Pharmacopoeia so as to achieve a concentration of 1.5% w/v. This solution was used as an external liquid phase. 150 ml of the external liquid phase was decanted into a tall 600 ml beaker and the internal phase prepared above was added thereto. Emulsification was achieved using a Silverson™ L-2R mixer, a lab-scale homgenizer, a full speed (6,000 r.p.m.) for 2 minutes and then dropping the speed as required to achieve the desired particle size.

The suspension of particles in the external phase was then introduced into a rotary evaporator and the acetone was removed under vacuum. The suspension now consisted solely of polymer coated theophylline or "pharmasomes" suspended in the external liquid phase. On microscopic examination the particle size of the "pharmasomes" was found to range from 10 to 180 μm.

The particles were centrifuged at 2500 r.p.m. for five minutes and the external phase was decanted. The particles were then washed four times with b 100 ml of heptane to remove the external liquid phase. The final product was then filtered over Whalton #4 paper and dried at 45° C. for two hours. The particles were then sieved with mesh sizes of 50, 90, 125 and 180 μm sieve.

The dissolution rate of the 90–125 μm fraction of the particles was estimated using the Paddle Method of U.S. Pharmacopoeia XX as indicated above. The results were as follows:

Time (h)	% Release
0.5	42
1	57
2	62
3	65
4	69
5	73
6	78
7	85
8	91
9	95
10	97

The particles were found to be tasteless with complete masking of the normally bitter taste of theophylline.

EXAMPLE 2

Preparation of micro-particles containing acetaminophen

Example 1 was repeated that 20 g of acetaminophen was used in place of 10 g of theophylline. In the external liquid phase heavy mineral oil was replaced by light mineral oil. A major proportion of the particles had an average size of 90 μm.

The dissolution rate of the particles was determined and was found to be as follows:

Time (h)	% Release
0	0
0.5	47
1	55
2	67
3	75
4	80
5	85
6	89
7	91
8	96

The particles were found to be tasteless.

EXAMPLE 3

Preparation of micro-particles containing nifedipine

Example 1 was repeated except that 16 g of nifedipine was used in place of theophylline. The internal phase consisted of Eudragit RS 100 TM (a product of Rohm and Haas) in methanol at a concentration of 33% w/v. The external phase consisted of magnesium stearate in light mineral oil at a concentration of 2.5% w/v.

The dissolution rate of the particles formed was determined and was found to be as follows:

Time (h)	% Release
0.5	25
1	30
2	35
3	55
4	70
6	85

The particles were tasteless.

EXAMPLE 4

Preparation of micro-particles containing dextromethorphan hydrobromide

Example 1 was repeated except that 10 g of theophylline was replaced by 10 g of dextromethorphan hydrobromide.

The dissolution rate of the particles was determined and was found to be as follows:

Time (h)	% Release
0.5	45
1	55
2	70
3	74
4	80
5	—
6	90

EXAMPLE 5

Preparation of micro-particles containing saccharin sodium

Example 1 was repeated except that theophylline was replaced by 6.5 g of saccharin sodium. The internal phase consisted of Ethocel TM (Dow Corning's trademarked ethyl cellulose product) 45 cps dissolved in ethanol to give a concentration of 15% w/v. Saccharin sodium was added to 50 g of the polymer solution. The external liquid phase consisted of heavy mineral oil U.S. Pharmacopoeia.

The dissolution rate of the particles was determined and was found to be as follows:

Time (min)	% Release
5	60
10	75
15	89
30	94
60	100

EXAMPLE 6

Preparation of micro-particles containing pseudoephedrine hydrochloride

The procedure of Example 1 was repeated except that theophylline was replaced by 10 g of pseudoephedrine hydrochloride. 50 g of CAB was used which was dissolved in 700 ml of hexane to form the polymer solution.

The dissolution rate of the particles was determined and found to be as follows:

Time (h)	% Release
0.5	35
1	55
2	60
3	68
4	73
5	80
6	84
7	90
8	94

EXAMPLE 7

Preparation of micro-particles containing carbinoxamine maleate

Example 1 was repeated except that theophylline was replaced by 5 g of carbinoxamine maleate. The dissolution rate of the particles was determined and found to be as follows:

Time (h)	% Release
0.5	20
1	25
2	30
3	45
4	55
5	65
6	70
7	73
8	78

EXAMPLE 8

Preparation of micro-particles containing guaiphenesin

Example 1 was repeated except that theophylline was replaced by guaiphenesin (12.5 g). The polymer solution consisted of Ethocel TM 4 cps dissolved in ether to give a concentration of 25% w/v.

The external phase consisted of an aqueous solution of sorbitol 70% w/w (sorbitol solution B.P.)

Upon removal of the solvent of the internal phase the particles or "pharmacomes" remained suspended in the sorbitol solution. The particles were harvested by decanting the sorbitol solution. The dissolution rate of the particles was determined and was found to be as follows:

Time (h)	% Release
0.5	50
1	55
2	61
3	64
4	70
5	76
6	81
7	87
8	93

EXAMPLE 9

Example 8 was repeated without decanting the sorbitol solution. The suspension thereby obtained was flavored and made up to the required strength for use as an oral suspension.

EXAMPLE 10

Preparation of micro-particles containing erythromycin base

Example 1 was repeated except that theophylline was replaced by erythromycin base. The polymer used was a mixture of cellulose acetate butyrate and cellulose acetate phthalate in a ratio of 2:1. The dissolution rate of the particles was determined and was found to be as follows:

Time (h)	% Release
0.5	20
1	30
2	40
3	55
4	70
5	78
6	87
7	95

Other mixed polymers were used in the internal phase and proved successful in achieving a 100% release of the active ingredient from the particles formed. Examples of mixed polymers used were as follows:

Polymer	Ratio
Cellulose acetate butyrate/ polyvinylpyrrolidone	9:1
Cellulose acetate butyrate/ polyvinylpyrrolidone	4:1
Cellulose acetate butyrate/ poly(methyl methacrylic acid)	1:1
Cellulose acetate butyrate/ Poly(methyl methacrylic acid)	3:1
Eudragit RS™/Eudragit RL™	9:1
Ethocel™/polyvinylpyrrolidone	9:1

EXAMPLE 11

Preparation of theophylline syrup

Particles prepared according to Example 1 were suspended in a sugar solution in water (66%) to obtain a theophylline syrup containing 200 mg of theophylline per 5 ml of syrup. When administered orally the normally bitter taste of theophylline was completely masked.

Pharmacological Data

The plasma level profile of theophylline was obtained from the mean values obtained for two subjects according to the data listed in Tables 1 and 2 below. FIG. 3 is a graph of plasma levels (mcg/ml) versus time after administration (hours) for the theophylline syrup based on the values indicated in Tables 1 and 2.

It will be observed from the accompanying FIG. 3 and Tables 1 and 2 that the plasma levels after 10 hours are not significantly different from the plasma levels after one hour. Accordingly, the graph shows a prolonged absorption phase with a minimum of fluctuation of plasma levels over 10 hours. Normally, theophylline (rapid or immediate release) peaks at 2 hours. The apparent biological half-life of thiophylline has been found to range from 4–9 hours. One would normally expect half the peak plasma levels by 7 hours and approximately one third of the peak plasma levels by 10 hours.

These results suggest that the syrup prepared according to Example 11 could potentially be dosed quite safely at intervals of 12 hours i.e. twice daily. This is half the dosage frequency of conventional non-sustained or immediate release theophylline.

TABLE 1

BLOOD LEVEL STUDY RESULTS - SUMMARY OF PHARMACOKINETIC DATA THEOPHYLLINE - 600 mg S.D. PLASMA LEVELS mcg/ml

	HOURS AFTER ADMINISTRATION					
SUBJ	0.00	1.00	2.00	4.00	6.00	8.00	10.00
1	0.00	3.15	4.25	4.70	3.45	3.00	2.85
2	0.00	2.90	4.85	5.05	5.00	4.30	4.25
MEAN	0.00	3.03	4.55	4.88	4.23	3.65	3.55
ST DEV	0.00	0.18	0.42	0.25	1.10	0.92	0.99
CV (%)*	0.00	5.84	9.32	5.08	25.94	25.18	27.89
MAX	0.00	3.15	4.85	5.05	5.00	4.30	4.25
MIN	0.00	2.90	4.25	4.70	3.45	3.00	2.85

*Coefficient of variation

TABLE 2

THEOPHYLLINE - 600 mg B.D.
PHARMACOKINETIC PARAMETERS

	AUC* (0.00-10.00 H)	PEAKING TIME T(max)	PEAK HEIGHT C(max)	C(max)/C(min) AT 10.00 HOURS	ELIMINATION RATE K EL	HALF-LIFE T ½
1	34.67	4.00	4.70	1.63	0.05	14.51
2	43.13	4.00	5.05	1.19	0.03	20.74
MEAN	38.90	4.00	4.88	1.42	0.04	17.62
ST DEV	5.98	0.00	0.25	0.33	0.01	4.21
CV (%)	15.36	0.00	5.08	22.91	25.00	25.00
BASED ON BLOOD LEVEL CURVE						
MEAN		4.00	4.88	1.37		

*Area under curve

EXAMPLE 12

Theophylline Suspension

Theophylline micro-particles"pharmasomes" (prepared as per Example 1) were suspended in a liquid vehicle consisting of:

70% Sorbitol Solution: 89.9% by weight
Glycerin: 10.0% by weight
Polysorbate-80 TM : 0.1% by weight

to give a suspension containing 200 mg theophylline per 5 ml.

Samples of the suspension were stored at room temperature and tested at intervals to determine the stability of the "pharmasomes" in suspension.

At the time of preparation the assayed content of theophylline was 188.4 mg/5 ml and after 15 weeks it was 190.5 mg/5 ml indicating that there had been no chemical breakdown of the drug.

The dissolution rate was also tested over a 15 week period and the results are summarized in Table 3 and FIG. 4.

In summary the data shows that the suspension retains its potency and dissolution characteristics for at least 15 weeks after preparation.

Pharmacological Data

The suspension prepared as per Example 12 was tested in a six subject bioavailability study at a dose of 720 mg (18 ml) versus a conventional syrup (Somophylline a product of Fisons) given as two doses of 360 mg at 0 and 6 hours. The results are summarized in Table 4 and FIG. 5. In FIG. 5 curve (a) represents the suspension of Example 12 and curve (b) represents the Somophylline syrup used as reference.

TABLE 3

THEOPHYLLINE SUSPENSION OF EXAMPLE 12 (200 mg/5 ml) STABILITY OF DISSOLUTION

	Percentage Dissolution TIME (HOURS)							
	0.00	1.00	2.00	3.00	4.00	5.00	6.00	24.00
0 wks	0.00	43.30	59.20	75.60	80.00	84.30	87.70	100.00
3 wks	0.00	39.50	59.10	70.70	77.90	84.20	87.70	99.50
5 wks	0.00	40.00	60.10	69.80	78.20	85.10	85.90	99.00
7 wks	0.00	42.00	63.00	79.20	84.20	90.00	90.60	100.00
15 wks	0.00	45.80	60.90	72.50	80.70	84.90	88.00	99.90

TABLE 4

MEAN THEOPHYLLINE PLASMA CONCENTRATION (mcg/ml)

TIME (h)	SOMOPHYLLINE	THEOPHYLLINE SUSPENSION
0.0	0.0	0.0
0.5	7.98	1.38
1.0	10.24	3.57
1.5	8.68	6.09
2.0	8.17	7.31
3.0	7.68	8.81
4.0	5.93	9.75
6.0	5.25	9.17
6.5	10.94	9.75
7.0	11.20	9.08
7.5	11.75	8.84
8.0	12.37	9.14
9.0	11.98	8.37
10.0	10.76	7.52
12.0	8.99	6.26

The data clearly shows that although the theophylline suspension of Example 12 is slightly less bioavailable (87%) than the reference, the time to peak and the duration of significant blood levels is indicative of a twice daily dosage regimen. The usual dosage regimen for theophylline is four times per day.

EXAMPLES 13 and 14

Theophylline micro-particle "pharmasomes" were prepared according to Example 1 and screened into two fractions:

Example 13—micro-particles having an average particle size of less than 90 microns;

Example 14—micro-particles having an average particle size of greater than 90 microns.

The "pharmasomes" were suspended in a vehicle made up of:

	% by weight
70% Sorbitol Solution	85.3
Avicel RC 591M	0.7
Potassium Sorbate	0.3
Titanium Dioxide 25% (in 70% Sorbitol)	2.7
Simethicone M 10% Emulsion	0.01
Glycerin	10.8
Citric Acid	0.3
Sodium Lauryl Sulphate	0.04

to produce a suspension containing 300 mg theophylline per 5 ml.

Pharmacological Data

The suspensions of Examples 13 and 14 were tested for bioavailability in four subjects at a dose of 690 mg

(11.5 ml) for the syrups of Examples 13 and 14 versus a conventional syrup (Somophylline a product of Fisons) given as two doses of 320 mg at 0 and 6 hours. The results are summerized in Table 5 and FIG. 6. In FIG. 6, curve (a) represents the suspension of Example 13, curve (b) the suspension of Example 14 and curve (c) the Somophylline syrup used as reference.

TABLE 5

MEAN THEOPHYLLINE PLASMA CONCENTRATIONS - mcg/ml

Time (h)	Somophylline	Suspension of Example 13	Suspension of Example 14
0	0	0	0
0.5	9.53	2.65	1.98
1	10.14	5.08	4.07
1.5	9.21	6.9[illegible]	6.45
2	8.64	7.16	6.81
3	7.74	6.93	7.67
4	6.82	7.74	7.99
6	5.21	6.46	7.08
6.5	8.79	—	—
7	12.00	6.74	6.93
7.5	12.01	—	—
8	12.11	6.03	6.47
9	11.61	—	—
10	10.17	5.35	5.82
12	8.07	4.06	5.02
15	—	2.77	4.04
18	—	2.22	2.67
21	2.44	1.79	1.95
24	1.55	1.28	1.59

The results confirm the findings for Example 12 as indicated in FIG. 7, wherein curve (a) represents the suspension of Example 12, curve (b) the suspension of Example 13 and curve (c) the suspension of Example 14.

EXAMPLE 15

Acetaminophen Suspension

Acetaminophen "pharmasomes" prepared as per Example 2 were suspended in a liquid vehicle prepared as per Example 12 to give a suspension containing 300 mg of acetaminophen per 5 ml.

The suspension was stored at room temperature and tested at certain intervals for 30 weeks.

At the time of preparation the assayed content was 299.8 mg (acetaminophen) per 5 ml and after 30 weeks was 297.9 mg/5 ml indicating that there was no significant loss of activity.

During the above time period the dissolution was also tested and the results are given in Table 6.

TABLE 6

PERCENTAGE DISSOLUTION

	TIME (h)						
	0.00	1.00	2.00	3.00	4.00	5.00	6.00
0 wks	0.00	56.50	70.60	76.00	81.30	83.80	86.30
2 wks	0.00	58.40	71.80	80.40	81.70	86.40	87.90
5 wks	0.00	56.90	72.50	77.20	80.40	83.90	84.40
7 wks	0.00	55.30	69.10	75.40	80.30	82.90	84.70
15 wks	0.00	58.90	69.30	76.78	80.60	82.80	84.20
30 wks	0.00	58.10	71.50	76.90	81.90	84.70	87.30

A graphic representation of these results is shown in FIG. 8.

The suspension was tested for bioavailability in 6 subjects at a dose of 1000 mg versus a reference solution (Dozol-Elixir TM a product of Rice Steele) which was given as two divided doses of 500 mg. The results are given in Table 7.

TABLE 7

MEAN ACETAMINOPHEN PLASMA CONCENTRATIONS (mcg/ml)

Time (h)	Reference (DOZOL)	Suspension of Example 15
0.0	0.0	0.0
0.5	7.74	3.44
1.0	6.49	6.05
2.0	4.14	7.36
3.0	3.04	5.80
4.0	2.04	4.60
6.0	1.08	3.15
6.5	5.33	2.65
7.0	5.88	2.26
8.0	4.79	1.88
9.0	4.00	1.63
10.0	3.05	1.44
12.0	1.81	1.06
14.0	1.10	0.72
16.0	0.69	0.49
24.0	0.18	0.14

A graphic representation is given in FIG. 9, wherein curve (b) represents the conventional Elixir and curve (a) represents the suspension of Example 15.

The data shows that although the suspension of Example 15 is slightly less bioavailable (90%) than the reference, the blood level is maintained for almost twice as long equating to halving of the dosage frequency.

EXAMPLE 16

"Pharmasoms" were prepared as per Example 2 and suspended in liquid as per Example 13 to give a suspension containing 320 mg per 5 ml. This suspension was tested for bioavailability in 6 subjects versus a conventional acetaminophen preparation (Tylenol TM Elixir a product of Johnson and Johnson) as reference. A single dose of acetaminophen "pharmasomes" 2000 mg (31.25 ml) was administered and two doses of Tylenol (1000 mg) were administered at 0 and 6 hours. The results are given in Table 8.

TABLE 8

MEAN ACETAMINOPHEN PLASMA CONCENTRATIONS (mcg/ml)

TIME (h)	Reference (Tylenol Elixir)	Suspension of Example 16
0.0	0.0	0.0
0.5	14.33	8.27
1.0	14.05	15.09
2.0	6.69	14.34
3.0	6.95	13.24
4.0	4.93	11.53
4.5	15.53	9.52
5.0	14.67	8.08
6.0	12.72	6.10
7.0	8.92	4.43
8.0	6.61	3.54
10.0	3.64	2.43
12.0	2.17	1.10
14.0	1.51	1.10
16.0	0.77	0.68
24.0	0.02	0.17

The results are presented graphically in FIG. 10 wherein curve (a) corresponds to the suspension of Example 16 and curve (b) corresponds to the reference Elixir. The prolonged absorption profile again can be seen with no significant loss in bioavailability, indicating a reduced dosage frequency.

EXAMPLE 17

"Pharmasomes" were prepared as per Example 2 with cellulose acetate being substituted for the cellulose acetate butyrate. The suspension was prepared as per Example 16. The suspension was tested in a 6 subject bioavailability study at a single dose of 2000 mg against a reference solution (Tylenol Elixir) given as two 1000 mg doses. The results are given in Table 9.

TABLE 9

MEAN ACETAMINOPHEN PLASMA CONCENTRATIONS (mcg/ml)		
TIME (h)	Tylenol Elixir 1 g × 2	Suspension of Example 17 2 g × 1
0.0	0.00	0.00
0.5	12.30	5.11
0.75	12.88	7.07
1.0	12.29	9.15
1.5	10.17	12.01
2.0	8.19	12.47
3.0	6.00	11.17
4.0	4.35	9.40
4.5	13.54	8.37
4.75	14.00	8.04
5.0	13.02	7.55
5.5	13.09	6.57
6.0	11.20	5.71
7.0	8.17	4.54
8.0	5.98	3.76
10.0	3.42	2.66
12.0	1.98	1.60
14.0	1.24	1.03
16.0	0.82	0.83
24.0	0.26	0.39

The figures given in Table 9 and accompanying FIGS. 11 and 12 again demonstrate the prolonged absorption nature of the product. In FIG. 11 curve (a) corresponds to the suspension of Example 19 and curve (b) corresponds to the reference Tylenol Elixir. In FIG. 12 curve (a) corresponds to the suspension of Example 15, curve (b) to the suspension of Example 16 and curve (c) to the suspension of Example 17.

EXAMPLE 18

Chewing gum containing micro-particles of Aspartame were prepared in the following manner.

An internal phase was prepared by dissolving ethylcellulose (45 cps) in sufficient ethanol to produce 200 g of solution. 100 g of Aspartame (particle size less than 60 microns) was dispersed in 300 g of acetone. The two liquids were then mixed by mechanical agitation. The external phase was prepared according to Example 1, 2 liters being required. The internal and external phase were mixed by mechanical agitation and then passed through an emulsifier. The emulsion was placed in a vacuum and the solvents (acetone and ethanol) evaporated. The aspartame/ethylcellulose micro-particles were harvested by centrifugation.

To evaluate the aspartame-containing "pharmasomes", unsweetened chewing gum was used. Pure aspartame powder and the prepared "pharmasomes" were folded into the gum to give a 0.2% concentration of aspartame. Both types of gum were chewed by a panel of 24 volunteers in a blind, crossover manner. The volunteers were asked to report their perception of the intensity (on a scale of 0 to 10) and duration of sweetness. On average the duration of sweetness for the pure aspartame-containing gum was 10 minutes. The gum containing the "pharmasomes" was perceived as being less intensely sweet but observably sweet for 30 minutes on average. The results are indicated in FIG. 13 which is a graphic representation of the aspartame sweetness test giving means values for the testing panel of 24 volunteers.

EXAMPLE 19

Chewable Tablet containing acetaminophen

The following materials were mixed together:

1000 g	Acetaminophen "pharmasomes" - as per Example 2 (equivalent to 500 g of acetaminophen)
250 g	Dipsoil (Sucrose 97%, Dextrins 3%)
250 g	Mannitol
5 g	Colloidal Silicon Dioxide
25 g	Maize Starch
20 g	Magnesium Stearate
15 g	Orange Flavor
35 g	Orange Color

The blend was compressed at a weight of 960 mg into tablets each containing 300 mg of acetaminophen. The tablets were pleasant to chew and the dissolution characteristics of the "pharmasomes" were uncharged as shown in Table 10 and FIG. 14.

TABLE 10

	DISSOLUTION RATE	
TIME (h)	"PHARMASOMES"	TABLETS
1	58.7%	59.2%
3	79.8%	80.7%
6	95.6%	95.8%

In FIG. 14 curve (a) corresponds to the dissolution pattern of the "pharmasomes" of Example 19 and curve (b) to the chewable tables prepared therefrom.

EXAMPLE 20

"Melt" Tablets Containing Acetaminophen

Melt tablets are similar to chewable tablets except that they disintegrate rapidly in the mouth and do not need to be chewed. Such tablets were prepared as follows:

1000 g	Acetaminophen "pharmasomes" (as per Example 2) (equivalent to 500 g acetaminophen)
50 g	Mannitol
250 g	Microcrystalline Cellulose
30 g	Strawberry Flavor
15 g	Red Color
60 g	Cross-Povidonesld
5 g	Sodium Lauryl Sulphate
30 g	Carboxymethyl Starch
15 g	Magnesium Stearate
15 g	Talc

The blends was compressed at a weight of 882 mg to give tablets each containing 300 mg of acetaminophen. The disintegration time of the tables was less than 30 seconds and the dissolution rate of the "pharmasomes" was unchanged as indicated in Table 11 and FIG. 15.

TABLE 11

	DISSOLUTION RATE	
TIME (h)	"PHARMASOMES"	TABLETS
1	58.7%	60.1%
3	79.8%	81.2%
6	95.6%	95.5%

In FIG. 15 curve (a) corresponds to the dissolution pattern for the "pharmasomes" of Example 20 and curve (b) to the melt tablets prepared therefrom.

EXAMPLE 21

Capsules Containing Nifedipine

"Pharmasomes" were prepared as per Example 3. By nature they were free flowing and only 0.5% magnesium stearate needed to be added to prevent sticking during capsule filling. The equivalent of 20 mg of nifedipine was encapsulated into size No. 4, two piece hard gelatin capsules. The dissolution rate remained unchanged as shown in Table 12 and FIG. 16. In FIG. 16 curve (a) corresponds to the dissolution pattern for the "pharmasomes" of Example 21 and curve (b) to the capsules prepared therefrom.

TABLE 12

	DISSOLUTION RATE	
TIME (h)	"PHARMASOMES"	CAPSULES
0.5	42.6%	41.7%
1	56.1%	54.9%
3	74.6%	73.6%
5	85.9%	84.4%
8	98.7%	97.6%

EXAMPLE 22

Non-Aqueous Suspension of Potassium Chloride

A non-aqueous suspension of potassium chloride-containing "pharmasomes" was prepared, having a concentration of potassium chloride of 300 mg/5 ml and which in addition to the "pharmasomes" contained the following ingredients:

Oil USP (Soy, cotton seed)	425.00 ml
Sorbitol Powder USP	100.00 g
Aerosil R 972M	12.50 g
Tenox GT 1M	0.20 g
Citric Acid	0.025 g
Chocolate flavor #396676	0.52 ml
Chocolate mint flavor #395496	0.37 ml
Flavor enhancer	1.00 g
Brown Lake dye	0.05 g
Titanium dioxide	0.10 g

The total volume of the suspension without the "pharmasomes" was 500 ml.

The Sorbitol powder USP and Aerosil R 972M (a product of Duphar, at Dutch company) were dry blended and then ball milled with the oil mix to produce an even dispersion. The Tenox GT 1M (a product of Tennessee Eastman Corp.) which is an anti-oxidant and the citric acid were dry blended and then dispersed with constant agitation into the oil mixture. The chocolate and chocolate mint flavors and the flavor enhancer were then dispersed into the oil mixture. Finally, the Brown Lake dye and the titanium dioxide were added to the oil mixture and the resultant mixture was agitated for one hour to ensure even dispersion of the various ingredients. An amount of potassium chloride-containing "pharmasomes", prepared according to the procedure described in Example 1 but substituting potassium chloride for theophylline, and equivalent to 300 mg potassium chloride per 5 ml was blended together with the oil mixture resulting in an evenly mixed suspension.

Although not wishing to be bound by any theoretical explanation of the invention, it is believed that the polymer substantially but not entirely coats the active ingredient, because a 100% release of active ingredient can be achieved even when an insoluble polymer is used.

While preferred embodiments of the invention have been shown and described, it will be understood by persons skilled in the art that various changes and modifications may be made thereto without departing from the spirit and scope thereof as defined by the following claims.

What is claimed is:

1. A controlled release taste masked powder containing discrete micro-particles for use in edible pharmaceutical and other controlled release compositions, said powder comprising particles containing an active ingredient in intimate admixture with at least one non-toxic insoluble, permeable, impermeable, or biodegradable controlled release polymer, or mixtures thereof, in an amount effective to provide a predetermined and controlled release of said active ingredient, each of said particles being in the form of a micromatrix with the active ingredient uniformly distributed throughout the matrix, but not entirely coated by the polymer, said particles having an average size of from 0.1 to 125 μm, being unlikely to be significantly degraded or ground by any chewing action, and having a predetermined release of said active ingredient.

2. A controlled release powder according to claim 1, wherein the particles have an average size of from 5 to 100 μm.

3. A controlled release powder according to claim 1 wherein the active ingredient is a drug, a nutrient, a flavoring agent or a sweetening agent.

4. A controlled release powder according to claim 1 wherein the active ingredient is a coloring agent, a fragrance, a herbicide or a pesticide.

5. A controlled release powder according to claim 1 wherein the polymer is selected from the group consisting of: alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, polymers of acrylic and methacrylic acids and esters thereof, polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes and polyurethanes and copolymers thereof.

6. A process for preparing a controlled release powder according to claim 1, which comprises the steps of:

(a) forming a solution of the polymer or polymers in a solvent;

(b) dissolving or dispersing the active ingredient in said polymer solution to form an uniform mixture; and

(c) removing the solvent from the mixture to obtain micro-particles having an average size of from 0.1 to 125 μm.

7. A process according to claim 6 wherein the particles obtained have an average size of from 5 to 100 μm.

8. A process according to claim 6 wherein the solvent is selected from the group consisting of: water, alcohols, ketones, halogenated aliphatic compounds, halogenated aromatic hydrocarbon compounds, aromatic hydrocarbon compounds and cyclic ethers or a mixture thereof, and the solvent is removed in step (c) by spray drying, use of an external liquid phase, phase separation, interfacial polymer deposition or coacervation.

9. A pharmaceutical composition containing a pharmaceutically effective amount of a controlled release powder according to claim 1.

10. A pharmaceutical composition containing a pharmaceutically effective amount of a controlled release powder according to claim 1 and which is in the form of tablets, capsules, suppositories, implants or ocular inserts.

11. A pharmaceutical composition according to claim 9 which is in the form of chewable tablets or melt tablets.

12. A pharmaceutical composition containing a pharmaceutically effective amount of a controlled release powder according to claim 1 and which is in the form of a cream, an ointment or a formulation suitable for transdermal delivery.

13. A pharmaceutical composition containing a pharmaceutically effective amount of a controlled release powder according to claim 1 and which is in the form of a liquid for oral, local or parenteral administration.

14. A pharmaceutical composition according to claim 12, which is in the form of eye drops, nasal drops, ear drops, a suspension, a syrup, or an infusion or injectable solution.

15. A pharmaceutical composition according to claim 9 wherein the active ingredient is selected from the group consisting of ibuprofen, actaminophen, 5-aminosalicyclic acid, dextromethorphan, propranolol theophylline, diltiazem, methyldopa, pseudoephedrine, cimetidine, cephalexin, cephaclor, cephradine, naproxen, piroxicam, diazepam, diclofenac, indomethacin, amoxycillin, pivampicillin, becampicillin, dicloxacillin, erythromycin, erythromycin stearate, lincomycin, codergocrine mesylate, doxycycline, dipyridamole, frusemide, triamterene, sulindac, nifedipine, atenolol, lorazepam, glibenclamide, salbutamol, trimethoprim/-sulphamethoxazole, spironolactone, carbinoxamine maleate, guaiphenesin, metoprolol tartrate and potassium chloride.

16. A pharmaceutical composition according to claim 9 for oral administration, wherein the active ingredient is theophylline.

17. A pharmaceutical composition according to claim 9 for oral administration, wherein the active ingredient is acetaminophen.

18. A pharmaceutical composition according to claim 9 for oral administration, wherein the active ingredient is potassium chloride.

19. An oral formulation for administration to human and non-human animal which is substantially free of the taste of the active ingredient comprising a controlled release powder according to claim 1.

20. An oral formulation according to claim 19 which is in the form of a liquid, chewable tablet, melt tablet, foam, gel or gum.

21. A chewable gum which contains as sweetening agent aspartame-containing micro-particles according to claim 1.

22. A non-aqueous suspension of a highly water-soluble or water-insoluble active ingredient, wherein the active ingredient is in the form of micro-particles of a controlled release powder according to claim 1.

23. A non-aqueous suspension according to claim 22 wherein the highly water-soluble active ingredient is selected from the group consisting of dextromethorphan, guaiphenesin and pseudoephedrine and salts thereof and potassium chloride.

24. A controlled release antibiotic formulation substantially free from the taste of said antibiotic for pharmaceutical or veterinary use which comprises a controlled release powder according to claim 1.

25. An antibiotic formulation according to claim 24 wherein the powder is in the form of a non-aqueous suspension.

26. An antibiotic formulation according to claim 24 which is in the form of a reconstitutable aqueous suspension.

27. A controlled release powder containing discrete micro-particles for use in edible, pharmaceutical and other controlled release compositions, said powder comprising particles containing an active ingredient in intimate admixture with at least one non-toxic polymer, wherein said polymer substantially but not entirely coats the active ingredient, each of said particles being in the form of a micromatrix with the active ingredient uniformly distributed throughout the matrix, said particles having an average size of from 0.1 to 125 μm, and a dissolution rate of active ingredient from said particles which is substantially proportional to the square root of time, said active ingredient selected from the group consisting of:

metoclopramide bromide, propantheline bromide, aluminium trisilicate, aluminum hydroxide, cimetidine, phenylbutazone, indomethacin, naproxen, ibuprofen, flurbiprofen, diclofenac, dexamethasone, prednisone, glyceryl trinitrate, isosorbide dinitrate, pentaerythritol tetranitrate, soloctidilum, vincamine, naftidrofuryl oxalate, co-dergocrine mesylate, cyclandelate, papaverine, nictoninic acid, erythromycin stearate, cephalexin, nalidixic acid, tetracycline hydrochloride, ampicillin, flucloxacillin sodium. hexamine mandelate, hexamine hippurate, flurazepam, diazepan, temazepam, amitryptyline, doxepin, lithium carbonate, lithium sulfate, chlorpromazine, thioridazine, trifluperazine, fluphenazine, piperothiazine, haloperidol, maprotiline hydrochloride, imipramine, desmethylimipramine, methylphenidate, ephedrine, epinephrine, isoproterenol, amphetamine sulfate, amphetamine hydrochloride, diphenhydramine, diphenylpyraline, chlorpheniramine, brompheniramine, bisacodyl, magnesium hydroxide, dioctyl sodium sulfosuccinate, ascorbic acid, alpha tocopherol, thiamine, pyridoxine, dicyclomine, diphenoxylate, verapamil, nifedipine, diltiazem, procainamide, disopyramide, bretylium tosylate, quinidine sulfate, quinidine gluconate, propranolol hydrochloride, guanethidine monosulphate, methyldopa, oxprenolol hydrochloride, captopril, hydralazine, ergotamine, epsilon aminocaproic acid, protamine sulfate, acetylsalicylic acid, acetaminophen, codeine phosphate, codeine sulfate, oxycodone, dihydrocodeine tartrate, oxycodeinone, morphine, heroin, nalbuphine, butorphanol tartrate, pentazocine hydrochloride, cyclazacine, pethidine, buprenorphine, scopolamine, mefenamic acirl, phenytoin sodium, sodium valproate, dantrolene sodium, tolbutamide, disbenase glucagon, insulin, triiodothyronine, thyroxine and propylthiouracil, furosemide, chlorthalidone, hydrochlorthiazide, spironolactone, triamterene, ritodrine, appetite fenfluramine hydrochloride, phentermine and diethylpropion hydrochloride, aminophylline, theophylline, salbutamol, orciprenaline sulphate, terbutaline sulphate, guaiphenesin, dextromethorphan, noscа-

pine, carbocisteine, cetylpyridinium chloride, tyrothricin, chlorhexidine, phenylpropanolamine, pseudoephedrine, dichloralphenazone, [illegible]razepam, promethazine theoclate, ferrous sulfate, folic acid and calcium gluconate, sulphinpyrazone, allopurinol and probenecid.

28. A controlled release powder according to claim 27, wherein the particles have an average size of from 5 to 100 μm.

29. A controlled release powder according to claim 27, wherein the active ingredient is a drug, a nutrient, a flavoring agent or a sweetening agent.

30. A controlled release powder according to claim 27, wherein the active ingredient is a coloring agent, a fragrance, a herbicide or a pesticide.

31. A controlled release powder according to claim 27, wherein the polymer is selected from the group consisting of: alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, polymers of acrylic and methacrylic acids and esters thereof, polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes and polyurethanes and copolymers thereof.

32. A process for preparing a controlled release powder according to claim 27, which comprises the steps of:

(a) forming a solution of the polymer or polymers in a solvent;

(b) dissolving or dispersing the active ingredient in said polymer solution to form a uniform mixture; and,

(c) removing the solvent from the mixture to obtain micro-particles having an average size of from 1.0 to 125 μm.

33. A process according to claim 32 wherein the particles obtained have an average size of from 5 to 100 μm.

34. A process according to claim 32 wherein the solvent is selected from the group consisting of: water, alcohols, ketones, halogenated aliphatic compounds, halogenated aromatic hydrocarbon compounds, aromatic hydrocarbon compounds and cyclic ethers or a mixture thereof, and the solvent is removed in step (c) by spray drying, use of an external liquid phase, phase separation, interfacial polymer deposition or coacervation.

35. A pharmaceutical composition containing a pharmaceutically effective amount of a controlled release powder according to claim 27.

36. A pharmaceutical composition containing a pharmaceutically effective amount of a control release powder according to claim 27 and which is in the form of tablets, capsules, suppositories, implants or ocular inserts.

37. A pharmaceutical composition according to claim 35 which is in the form of chewable tablets or melt tablets.

38. A pharmaceutical composition containing a pharmaceutically effective amount of a controlled release powder according to claim 27 and which is in the form of a cream, an ointment or a formulation suitable for transdermal delivery.

39. A pharmaceutical composition containing a pharmaceutically effective amount of a controlled release powder according to claim 27 and which is in the form of a liquid for oral, local or parenteral administration.

40. A pharmaceutical composition according to claim 38, which is in the form of eye drops, nasal drops, ear drops, a suspension, a syrup, or an infusion or injectable solution.

41. A pharmaceutical composition according to claim 35 wherein the active ingredient is selected from the group consisting of ibuprofen, acetaminophen, 5-aminosalicylic acid, dextromethorphan, propranolol, theophylline, diltiazem, methyldopa, pseudoephedrine, cimetidine, cephalexin, cephaclor, cephradine, naproxen, piroxicam, diazepam, diclofenac, indomethacin, amoxycillin, pivampicillin, bacampicillin, dicloxacillin, erythromycin, erythromycin stearate, lincomycin, codergocrine mesylate, doxycycline, dipyridamole, frusemide, triamterene, sulindac, nifedipine, atenolol, lorazepam, glibenclamide, salbutamol, trimethoprim/sulphamethoxazole, spironolactone, carbinoxamine maleate, guaiphenesin timolol tartrate and potassium chloride.

42. A pharmaceutical composition according to claim 35 for oral administration, wherein the active ingredient is theophylline.

43. A pharmaceutical composition according to claim 35 for oral administration, wherein the active ingredient is acetaminophen.

44. A pharmaceutical composition according to claim 35 for oral administration, wherein the active ingredient is potassium chloride.

45. An oral formulation for administration to human and non-human animals which is substantially free of the taste of the active ingredient comprising a controlled release powder according to claim 27.

46. An oral formulation according to claim 45 which is in the form of a liquid, chewable tablet, melt tablet, foam, gel or gum.

47. A chewable gum which contains as sweetening agent aspartame-containing micro-particles according to claim 27.

48. A non-aqueous suspension of a highly water-soluble or water-insoluble active ingredient, wherein the active ingredient is in the form of micro-particles of a controlled release powder according to claim 27.

49. A non-aqueous suspension according to claim 48 wherein the highly water-soluble active ingredient is selected from the group consisting of dextromethorphan, guaiphenesin and pseudoephedrine and salts thereof and potassium chloride.

50. A controlled release antibiotic formulation substantially free from the taste of said antibiotic for pharmaceutical or veterinary use which comprises a controlled release powder according to claim 27.

51. An antibiotic formulation according to claim 50 wherein the powder is in the form of a non-aqueous suspension.

52. An antibiotic formation according to claim 50 which is in the form of a reconstitutable aqueous suspension.

* * * * *

United States Patent [19]

Yeh et al.

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[45] Date of Patent: Jul. 16, 1991

A3

[54] COMPOSITIONS AND METHOD FOR THE TREATMENT OF DISEASE

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[52] U.S. Cl. 424/49; 424/435; 424/443; 514/900; 514/902

[58] Field of Search 424/49-58, 424/443, 435; 514/900, 902

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[57] ABSTRACT

Synergistic compositions comprising an antioxidant and an arylpropionic, non-steroidal anti-imflammatory drug used to treat certain diseases are disclosed. The compositions inhibit production of arachidonic acid cascade end-products which have been implicated as causes of tissue-destruction in periodontal disease. The compositions are administered in combination with a carrier, which may be a mucosal-tenacious polymer selected from the groups of semi-solid pastes, gels, ointments, liquids or films.

12 Claims, No Drawings

COMPOSITIONS AND METHOD FOR THE TREATMENT OF DISEASE

BACKGROUND OF THE INVENTION

Periodontal disease is an inflammatory disorder of the supporting tissue of teeth. Without control, chronic inflammatory condition associated with periodontal disease will destroy tissue supporting teeth and eventually result in teeth loss.

Attempts have been made to alleviate periodontal disease using chemical agents. For example, U.S Pat. No. 4,789,662 to Thomas-Leurquin et al. discloses a pharmaceutical composition including collagen and a chlorhexidine antiseptic and anti-inflammatory substance. However, the traditional mode of prevention and treatment of periodontal disease has centered on maintaining good oral hygiene. This consists of, among other things, removal of dental plaque which is considered to be the etiological cause of dental caries and periodontal disease. Dental plaque consists of microbial masses which deliver a stream of enzymes, endotoxins and exotoxins onto gingival and marginal periodontal tissue leading to inflammation. The resulting inflammatory response triggers a series of catabolic processes. Specifically, as tissue reacts to protect itself from these toxic assaults, complex changes occur in the immune system in the function of osteoclasts, in the activity of lymphocytes in the blood streams, and in other bodily defenses. These changes and complement activation lead to increased prostaglandin formation at the inflammation site.

Prostaglandin, and related compounds, are principally formed by body cells at the site of tissue injury by a process known as arachidonic acid cascade This process occurs when essential fatty acids, especially linoleic acid, are enzymatically converted into arachidonic acid, which in turn is further metabolized through either the cyclooxygenase or lipoxygenase pathways to prostaglandins (PGS).

Prostaglandins, particularly prostaglandin-E_2 (PGE_2), have been implicated as components of the inflammatory reaction. Goodson et al., Prostaglandins, 6, 81-85 (1984) and El Attar et al., J. Periodontal, 52, 16-19 (1981) demonstrated that PGE_2 levels are elevated in inflamed gingiva when compared to normal gingiva. Offenbacher et al., J. Periodont. Res., 21, 101-112 (1986) demonstrated that extremely high levels of PGE_2 are present at periodontal sites of active attachment loss and low at sites which are in remission, i.e. there is no longitudinal attachment loss. The PGE_2 level in diseased tissue approximates 1 uM (Offenbacher et al., J. Periodon. Res. 19, 1-13 (1984)) which is a pharmacologically active concentration when tested in various model systems to induce vasodilation, bone resorption and other pro-inflammatory responses.

Despite this evidence regarding the key role of PGE_2 in the pathogenesis of periodontal disease, there has been substantially little appreciation of the use of drugs which inhibit PGE_2 synthesis in an attempt to retard or prevent periodontal tissue destruction.

SUMMARY OF THE INVENTION

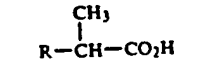
Accordingly, it is an object of the invention to provide new compositions and a method which inhibit prostaglandin formation and are therefore useful for the treatment of periodontal disease.

These and other objectives are achieved by providing a synergistic composition which comprises an antioxidant in combination with an arylpropionic, non-steroidal anti-inflammatory drug (NSAID) The antioxidant is preferably alpha-tocopherol, ascorbic acid or pharmaceutically acceptable salts thereof, or Vitamin A and its precursers including beta-carotene. The arylpropionic NSAID is preferably an alpha-arylproprionic NSAID, most preferably, ibuprofen, flurbiprofen, ketoprofen, fenoprofen or naproxen. The antioxidant and NSAID are combined with a pharmaceutically acceptable carrier The compositions are preferably formed into a laminate occlusive dressing, tablet capsule, pill, solution, gel suspension, or the like. In these types of formulations, antioxidant is preferably present in the composition in the range from about 0.01 to 10% by weight, and most preferably 0.03 to 2% by weight. NSAID is preferably present in the composition in the range from about 0.01 to 10% by weight and most preferably 0.01 to 2% by weight. Alternately, the composition may be compounded in a mucosal-tenacious polymer, preferably a water soluble or water dispersible karaya gum, ethylene oxide polymer, sodium carboxymethylcellulose or lower alkyl vinyl ether-maleic acid anhydride copolymer. The polymer, having the therapeutically effective composition therein, can be applied directly to the gingival tissues.

DETAILED DESCRIPTION OF THE INVENTION

Antioxidants reduce the oxidation of arachidonic acid by competing for enzymatically formed oxygen radicals during arachidonic acid cascade. The result of this competition is a decrease of prostaglandin synthesis and a concomitant decrease in plaque-induced gingival inflammation in addition to the tissue destruction which is associated therewith. Non-steroidal anti-inflammatory drugs (NSAID) treat inflammation, but have limited effectiveness in fighting the underlying disease origins of the inflammation.

According to the present invention, it has been discovered that the combination of one or more antioxidants and one or more arylpropionic, non-steroidal anti-inflammatory drugs produces a synergistic result in the treatment of inflammatory diseases, and in particular periodontal disease, by the reduction or prophylaxis of prostaglandin formation at the inflammation site. Preferably, the antioxidants are alpha-tocopherol, ascorbic acid or pharmaceutically acceptable salts thereof, or Vitamin A and its precursers including beta-carotene. Other antioxidants may be utilized in the present invention The NSAID is preferably an arylpropionic compound, preferably an alpha-arylproprionic acid or pharmaceutically acceptable salts thereof. Such compounds may be represented by the following formula



where R is an aromatic group and the compound possesses anti-inflammatory properties. Most preferably, the alpha-arylpropionic acid is ibuprofen, flurbiprofen, ketoprofen, fenoprofen, or naproxen.

In the determination of the synergistic activity of the compositions according to the present invention, the following in vitro testing was affected. A large pool of

inflamed human gingival tissue was obtained from patients with periodontitis who were undergoing routine periodontal surgery. The tissues were immediately stored in liquid nitrogen prior to use or were used fresh. The assay of cyclooxygenase products was performed as a modification of the assay of El Attar et al., J. Periodon. Res., 21, 169-176 (1986). Pooled tissue was weighed and homogenized at 0°-4° C. with a Polytron® (Brinkman) homogenizer in a 0.2 M TRIS buffer, pH 8.0, at a final concentration of 20 mg/ml. After centrifugation for 10 minutes at 1200×g, the supernatant was divided into 3 ml aliquots for incubation in the presence or absence of a test compound.

The test compounds were tested in triplicate over a concentration range of 10^{-8} to 10^{-14} M. For example, alpha-tocopherol from 10^{-12} to 10^{-} M was coupled with ketoprofen from 10^{-8} to 10^{-14} M range in a total of 3×7 matrix combinations in order to determine the synergistic effect as well as the IC_{50} (dosage concentration to reach 50% inhibition) of the combination.

Prostanoids were extracted as described by Powell, Methods in Eng., 86, 467 (1982) using a Sep-Pak-C_{18} cartridge from Waters Associates. The Sep-Pak was prepared by the sequential elution of 20 milliliters of ethanol and 20 milliliters of water. The sample was then adjusted to 15% ethanol, pH 3.0, with acetic acid and applied to the column. The column was eluted with 20 ml of 15% ethanol, pH 3.0, 20 ml of petroleum ether and then the prostaglandin Tx (thromboxane) was eluted with 10 ml of methyl formate. Thereafter, the methyl formate was evaporated to dryness with nitrogen and reconstituted in 32% acrylonitrile (high pressure liquid chromatography buffer).

Previous experience had revealed that the recovery was greater than 92% from PGE_2, PGI_2 (as 6KFl), TxA_2 (as TxB_2) and PGF_2. These are readily separated and quantified using a 4.6×100 nm RP-18 Spheri-5u column from Brownle Labs. A Flow-One radioactivity monitor simultaneously measured radioactivity while monitoring elution at 192 nanometers.

The net incorporation of the 14_C arachidonate was measured in the absence of the test substance in order to determine the maximum activity of the cyclooxygenase cascade.

The following Table 1 indicates the percent of control (maximum) PGE_2 synthesis as a function of alpha-tocopherol and ketoprofen concentration.

TABLE 1

	Percent of PGE_2 Synthesis In Presence of Ketoprofen and Alpha-Tocopherol						
	Ketoprofen Concentration (M)						
Alpha-tocopherol Concentration (M)	10^{-14}	10^{-13}	10^{-12}	10^{-11}	10^{-10}	10^{-9}	10^{-8}
At 10^{-14}M	102	129	116	131	112	75	97
At 10^{-13}M	105	68	101	82	62	61	36
At 10^{-12}M	66	68	41	62	48	51	49

As can be seen from Table 1, the exemplary composition of alpha-tocopherol and ketoprofen in combination resulted in a synergistic effect in the inhibition of PGE_2. Specifically, alpha-tocopherol lowered the IC_{50} value of ketoprofen and ketoprofen lowered the IC_{50} value of alpha-tocopherol.

In carrying out the method of the present invention, the antioxidant and arylpropionic, NSAID composition can be combined with a pharmaceutically acceptable carrier and administered orally, topically or bucally to the patient in need of treatment. Suitable forms of administration of the composition are forms such as laminate occlusive dressings, tablets, capsules, pills, solutions, gels, suspensions and the like.

The compositions of the present invention include an effective periodontal disease reducing amount of the antioxidant and NSAID in combination with the pharmaceutically acceptable carrier. The amount of active ingredients in the composition are about 0.01 to 10% by weight for the antioxidant and about 0.01 to 10% by weight for the arylpropionic, NSAID. The preferred weight % are about 0.03 to 2.0% for the antioxidant and about 0.01 to about 2.0% for the arylpropionic, NSAID. The carriers may include other materials such as lubricants, e.g., stearic acid or magnesium stearate, fillers such as lactose, sucrose and corn starch, desegregating agents such as algeic acid, surface active agents for use in injectable solutions or suspensions, and the like.

According to another embodiment of the invention, the synergistic compositions may be compounded into a carrier which has a strong and continuing adherence to the oral gingival mucosa. The carrier may then be applied to gingival tissues for two hours or longer in order to achieve a protracted topical therapeutic effect. Compositions of preferred vehicles which have acceptable properties are described herein as "mucosal-tenacious" and may be created from a variety of water-soluble or water-dispersible polymeric materials combined with other adjuvants.

All such materials used in the vehicle however, must have certain properties in common which are summarized below:

(1) They must be virtually non-toxic systemically.

(2) They must not irritate or damage bodily tissues at the site of the application.

(3) They must be water-soluble or water-dispersible polymeric molecules.

(4) They must be chemically and physically compatible with the synergistic composition.

(5) They must have a strong and persistent adherence to oral mucosal tissues, preferably for a minimum of 2 hours after application to affected tissues.

(6) They must allow the slow diffusion of the synergistic composition from the vehicle so that it can contact and permeate the mucosa at the site of application for protracted periods of time.

(7) They must be readily removable from the site of application by use of mild mechanical abrasion and a non-toxic detergent solution.

The mechanism by which a polymeric material bonds to oral mucosal tissues is complex. It is believed that chemical, physical and mechanical bonds form as permeation of molecules takes place into the irregularly contoured surface of the mucosal substrate. Since all body cells in vertebrate animals carry a net negative surface charge and most polymeric agents carry a net positive charge, an electrostatic bond develops due to

coulombic attractions, van der Waal forces, hydrogen bonding and covalent bonding.

There are a number of polymeric agents which can be employed to prepare mucosal-tenacious vehicles with the seven required attributes enumerated above. Among these are natural gums, plant extracts, animal extracts, cellulose derivatives, polyvinyl alcohols, polyvinylpyrrolidone, polycarbophil, polyacrylic acid derivatives, polyacrylamides, ethylene oxide homopolymers, polyethelene-polypropylene copolymers, polyethylenimines and others.

It is important in selecting a composition for the mucosal-tenacious vehicle that it allow the slow diffusion of the synergistic composition from the vehicle and into contact with the gingival tissues so that it can be absorbed into those tissues where it will induce its beneficial effects.

The chemical structures of the polymeric agent selected for use in the mucosal-tenacious vehicle of this invention are not nearly as important as their physical properties and ability to satisfy the seven conditions set forth above. However, a large number of materials can be selected which do satisfy these criteria if properly compounded at suitable concentrations into a vehicle such as a semi-solid paste, gel, liquid, ointment or film.

Among such agents are a number of natural hydrophilic polymeric agents, which are enumerated below:

(1) Agar, which is a hydrophilic colloid extracted from certain algae. It is relatively insoluble in cold water but soluble in hot water.

(2) Algin is derived from a brown algae, principally microcystitis pyriera. It is a linear polymer of high molecular weight; it is extracted principally as alginic acid and readily forms water-soluble alkali metal derivatives, amine derivatives and esters, all of which can be used in accordance with the teachings of this invention.

(3) Carageenan is another algae-derived water-soluble polymer and exists principally as the lambda, kappa and iota isomers.

(4) Other water-soluble polymers also derived from marine algae include fucoidan, laminoran and furcellaran.

(5) Gum arabic, also commonly called gum acacia, is the dried, gummy exudate of the acacia tree, indigenous to Africa, India, Central American and Southwest North America. It readily forms coacervates with gelatin.

(6) Gum ghatti is another tree exudate which has a higher viscosity in aqueous solutions than gum arabic.

(7) Gum karaya is a tree exudate with a high potential for water absorption and a relatively low pH. At concentrations of 5%-20%, it is a strong wet adhesive.

(8) Gum tragacanth is widely used in food processing and is obtained from a perennial shrub found in the Near East.

(9) Guar gum is obtained from the guar plant in India and Pakistan and forms viscous, colloidal dispersions in water.

(10) Locust bean gum is derived from the fruit of the carob tree, an evergreen found principally in Southern Europe.

(11) Other natural gums derived from the fruit of the carob tree, an evergreen found principally in southern Europe.

(12) Pectin is a general term for a group of water-soluble and water-dispersible polysacharides present in the cell walls of all plant tissues.

(13) A relatively recent type of water-soluble, natural polymer is that produced as an extracellular polysaccharide by bacteria or fungi. Included among these are xanthan gum, polysaccharide Y-1401, scleroglucan and various dextrans.

There are also some starch derivatives which meet many of the criteria outlined for a mucosal-tenacious, water-soluble or water-dispersible polymer above, but are not usable in this invention because of their susceptibility to amylolytic degradation from the enzyme ptyalin found in saliva.

In addition to the natural hydrophilic polymers, the following synthetic polymers may also be used:

1. Chemical modification of cellulose provides many derivatives which are useful within the teachings of this invention. Among these are methyl cellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylethylcellulose, hydroxypropyl cellulose; and ethylhydroxyethyl cellulose. These agents can be prepared in a wide range of solubility and viscosity ranges.
2. Polyvinyl alcohol is produced by the alcoholysis of polyvinyl acetate and can be made in a number of molecular weights, water-solubility ranges and viscosity ranges.
3. Polyvinylpyrrolidone is a homopolymer of N-vinylpyrrolidone with a high level of water solubility and pronounced viscosity-building properties.
4. Polyacrylic acid derivates can be used directly but more often are used with other copolymers; an important polyacrylic acid copolymer is polycarbophil.
5. Particularly useful materials are the partial calcium/-sodium salts of lower alkyl vinyl-maleic acid anhydride copolymers, sold commercially as "Gantrez" and "Ucarset".
6. Polyacrylamide is a polymer of acrylamide and can be polymerized by a variety of synthetic approaches.
7. Ethylene oxide polymers of very high molecular weight are commercially sold by the Union Carbide Co. as water-soluble resins ("Polyox"). They range in molecular weight from a few hundred thousand to five million or more. The higher molecular weight derivatives have extraordinary viscosity-building effects in water and other solvents, as well as pronounced mucosal-tenacity.
8. Polyethylenimines are produced from the monomer ethylenimine in the presence of an acid catalyst. They are of special interest for adherent formulations because of their tendency to form strong electrostatic bonds.

It is also possible to use at least one material of animal origin:

1. Gelatin is a partially hydrolized protein derived from the skin, connective tissues and bones of mammalian animals; that derived by acid treatment is Type A and that from alkali treatment is Type B.

These various polymeric materials herein described are illustrative of the many agents from which a composition can be compounded into useful mucosal-tenacious carriers. They may be used singly or in combination, in a wide range of concentrations, and in the presence of many other agents intended to control rates of water absorption and swelling, ingredients to enhance tissue penetration, various fillers, buffers, sweeteners, flavors, bodying agents and other pharmaceutical necessities.

Generally, such compositions include about 0.01 to about 10 parts antioxidant, about 0.01 to 10 parts aryl-propionic, NSAID, and about 20 to about 60 parts mucosal-tenacious polymer.

Examples 1-7 below are illustrative of pharmaceutically acceptable carriers with synergistic compositions therein which can be used in accordance with the teachings of the invention.

EXAMPLE 1

Components	% By Weight
1. CMC 7H3SXF (Sodium Carboxymethylcellulose)	10.0
2. Polyox (Polyethylene Oxide)	20.0
3. Polycarbophil	10.0
4. Calcium Oxide	1.0
5. Ketoprofen	1.0
6. Alpha-tocopherol	1.0
7. Polyvinylacetate	23.0
8. Triacetin	34.0
	100.0

Polyvinylacetate and triacetin were pre-mixed in a sigma-blade mixer. CMC 7H3SXF, polyox powder, polycarbophil, calcium oxide and ketoprofen were homogeneously mixed in a Tekmar mixer, followed by the addition of alpha-tocopherol at 1000 rpm Finally, the polyvinylacetate/triacetin pre-mix was added to the mixture, and resulted in a smooth cream-type product.

EXAMPLE 2

Components	% By Weight
1. Mineral Oil	51.45
2. CMC 7H3SXF (Sodium Carboxymethylcellulose)	32.0
3. Polyox (Polyethylene Oxide)	13.0
4. Propylparaben	0.05
5. Sodium Monophosphate	0.10
6. Flavor (Spray Dried)	0.40
7. Ketoprofen	2.0
8. Alpha-tocopherol	1.0
	100.0

Mineral oil was heated to 65° C. ion a Kitchen-Aid Bowl. CMC 7H3SXF, polyox, propylparaben and sodium monophosphate were slowly charged to the bowl and mix-homogeneously for 10–15 minutes. Finally the active agents (alpha-tocopherol and ketoprofen) and flavor were added and mixed thoroughly.

EXAMPLE 3

Components	% By Weight
1. Ethanol	15.0
2. Glycerin	15.0
3. Polysorbate	1.0
4. Sodium Lauryl Sulfate	0.1
5. Ketoprofen	1.0
6. Alpha-tocopherol	1.0
7. Flavor	0.1
8. Colorant (FD&C Grade)	0.005
9. Water	66.795
	100.0

Active agents (alpha-tocopherol and ketoprofen) were mixed homogeneously with ethanol in a container. In another container, flavor, glycerin, sodium lauryl sulfate, colorant and polysorbate were mixed together, followed by the addition of water. The ethanol (and active agents) solution was then charged to the aqueous portion and mixed thoroughly.

EXAMPLE 4

Components	% By Weight
1. Ethylene Oxide Homopolymer	40.0
2. Folyvinylpyrrolidone	40.0
3. Polyethylene Glycol 4000	14.9
4. Glycerin	1.0
5. Ketoprofen	2.0
6. Alpha-tocopherol	2.0
7. Flavor	0.1
	100.0

The first four ingredients are homogenized into an intimate mixture and warmed to about 40° C. The active agents and flavor were incorporated into the mixture and mixed thoroughly. The final mixture was cooled to about 25° C. and then extruded through stainless steel rollers into a film approximately 2 mm thick.

Components	% By Weight
1. Ketoprofen	2.0
2. Alpha-tocopherol	2.0
3. Hydrated Silica	12.0
4. Sorbitol Solution	12.0
5. Glycerin	12.0
6. Xanthan Gum	1.5
7. Fumed Silica	2.0
8. Flavor	0.5
9. Propyl Paraben	0.05
10. Methyl Paraben	0.05
11. Sodium Lauryl Sulfate	1.5
12. Water	54.4
	100.0

In a mixing vessel container fitted with a vacuum system and mixing apparatus, water, active agents, parabens, flavor, sorbitol solution, and silica were charged and mixed thoroughly. In a separate container xanthan gum was charged and mixed in glycerin and then charged to the mixing vessel. It was then mixed for about 10 minutes, detergent was added, and finally mixed under full vacuum for 20–30 minutes.

EXAMPLE 6

Components	% By Weight
1. Lactose	57.0
2. Avicel (pH 101)	33.0
3. Starch	4.0
4. Fumed Silica	1.0
5. Stearic Acid	2.0
6. Alpha-tocopherol	2.0
7. Ketoprofen	1.0
	100.0

Active ingredients (alpha-tocopherol and ketoprofen) were mixed homogeneously with lactose in a Ribbon mixer followed by the addition of Avicel, starch, fumed silica and finally stearic acid. Manesty equipment was used to produce tablets (average weight: 500 mg.).

EXAMPLE 7

Components	% By Weight
1. Lactose	80.0

-continued

Components	% By Weight
2. Starch	17.0
3. Alpha-tocopherol	1.0
4. Ketoprofen	1.0
5. Fumed Silica	1.0
	100.0

Alpha-tocopherol was homogeneously dispersed with lactose in a Ribbon Mixer, followed by ketoprofen, starch and fumed silica. After the powder was homogeneously mixed, it was then filled into hard gelatin capsules at an average weight of 500 mg. using an MG-2 automatic capsule filling machine.

Examples 8-9 below are also illustrative of mucosal-tenacious vehicles, with a synergistic composition incorporated therein, which can be used in accordance with the teachings of the present invention.

EXAMPLE 8

Components	% By Weight
1. CMC 7H3SXF (Sodium Carboxymethylcellulose)	10
2. Polyox WSR 301 (polyethylene oxide)	15
3. Polycarbophil	15
4. Calcium Oxide	1
5. Ibuprofen	1
6. Beta-carotene	1
7. Polyvinyl acetate	23
8. Triacetin	34
	100.0

Polyvinyl acetate and triacetin were pre-mixed in a Sigma-blade mixer. CMC7H3SXF, Polyox powder, polycarbophil, calcium oxide and ibuprofen were homogeneously mixed in a Tekman mixer, followed by the addition of Beta-carotene at 1000 rpm. Finally, a polyvinyl acetate/triacetin pre-mix was added to the mixture, and resulted in a smooth cream-type product.

EXAMPLE 9

Components	% By Weight
1. Ethylene Oxide Homopolymer	41.0
2. Polyvinylpyrrolidone	40.0
3. Polyethylene Glycol 4000	14.9
4. Glycerin	1.0
5. Ibuprofen	2.0
6. Beta-carotene	1.0
7. Flavor	0.1
	100.0

The first four ingredients are homogenized into an intimate mixture and warmed to about 40° C. The active agents and flavor were incorporated into the mixture and mixed thoroughly. The final mixture was cooled to about 25° C. and then extruded through stainless steel rollers into a film approximately 2 mm thick.

Although the present invention has been described in connection with preferred embodiments thereof, many other variations and modifications will now become apparent to those skilled in the art without departing from the scope of the invention.

What is claimed is:

1. A method for the treatment of periodontal disease comprising topically administering an effective periodontal disease reducing amount of a composition comprising a synergistic combination of alpha-tocopherol and ketoprofen or a pharmaceutically acceptable salt thereof in a pharmaceutically acceptable carrier to a host in need thereof, wherein the effective periodontal disease reducing amount of the alpha-tocopherol is from about 0.01 to 10% by weight and the effective periodontal disease reducing amount of the ketoprofen is from about 0.01 to 10% by weight, and wherein the amount of alpha-tocopherol is sufficient to lower the IC_{50} value of the ketoprofen and the amount of ketoprofen is sufficient to reduce the IC_{50} value of alpha-tocopherol, and wherein the carrier is a semi-solid paste, gel, liquid, ointment or film which has a strong and continuing adherence to the oral gingival mucosa.

2. A method as claimed in claim 1, wherein the carrier comprises a water soluble or water dispersible polymer.

3. A method as claimed in claim 2, wherein the polymer is selected from the group consisting of karaya gum, ethyleneoxide polymer, sodium carboxymethylcellulose and lower alkyl vinyl ether-maleic acid anhydride copolymer.

4. A synergistic composition for the treatment of periodontal disease comprising an effective periodontal disease reducing amount of alpha-tocopherol and ketoprofen or a pharmaceutically acceptable salt thereof in combination with a topical pharmaceutically acceptable carrier wherein the effective periodontal disease reducing amount of the alpha-tocopherol is from about 0.01 to 10% by weight and the effective periodontal disease reducing amount of the ketoprofen is from about 0.01 to 10% by weight, and wherein the amount of alpha-tocopherol is sufficient to lower the IC_{50} value of the ketoprofen and the amount of ketoprofen is sufficient to reduce the IC_{50} value of alpha-tocopherol, and wherein the carrier is a semi-solid paste, gel, liquid, ointment or film which has a strong and continuing adherence to the oral gingival mucosa.

5. A composition as claimed in claim 4, wherein the effective periodontal disease reducing amount of the alpha-tocopherol is from about 0.03 to 2.0% by weight and the effective periodontal disease reducing amount of the ketoprofen is from about 0.01 to 2% by weight.

6. A composition as claimed in claim 4, wherein the carrier comprises a water soluble or water dispersible polymer.

7. A composition as claimed in claim 6, wherein the combination of the composition and the carrier comprises about 0.01 to 10 parts alpha-tocopherol, and about 0.01 to 10 parts ketoprofen and about 20 to 60 parts polymer.

8. A composition as claimed in claim 7, wherein the polymer is selected from the group consisting of karaya gum, ethyleneoxide polymer, sodium carboxymethylcellulose and lower alkyl vinyl ethermaleic acid anhydride copolymer.

9. A composition as claimed in claim 4 comprising alpha-tocopherol and ketoprofen in a creme carrier comprising a polyacrylic acid polymer.

10. A composition as claimed in claim 1 in which the composition comprises alpha-tocopherol and ketoprofen in a creme carrier comprising a polymacrylic acid copolymer.

11. A method as claimed in claim 1 wherein the effective periodontal disease reducing amount of the alpha-tocopherol is from about 0.03 to 2.0% by weight and the effective periodontal disease reducing amount of the ketoprofen is from about 0.01 to 2% by weight.

12. A method as claimed in claim 2 wherein the combination of the composition and the carrier comprises about 0.01 to 10 parts alpha-tocopherol, and about 0.01 to 10 parts ketoprofen and about 20 to 60 parts polymer.

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CHAPTER 90

A4

Coating of Pharmaceutical Dosage Forms

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Any introduction to tablet coating must be prefaced by an important question—"Why coat tablets?"—since in many instances, the coating is being applied to a dosage form that already is functionally complete. In attempting to answer this question, if one examines the market, it immediately will be obvious that a significant proportion of pharmaceutical solid dosage forms are coated. The reasons for this range from the esthetic to a desire to control the bioavailability of the drug, and include:

1. Protecting the drug from its surrounding environment (particularly air, moisture and light) with a view to improving stability.
2. Masking of unpleasant taste and odor.
3. Increasing the ease by means of which the product can be ingested by the patient.
4. Improving product identity, from the manufacturing plant, through intermediaries and to the patient.
5. Facilitating handling, particularly in high-speed packaging/filling lines, and automated counters in pharmacies, where the coating minimizes cross-contamination due to dust elimination.
6. Improving product appearance, particularly where there are noticeable visible differences in tablet core ingredients from batch to batch.
7. Reducing the risk of interaction between incompatible components. This would be achieved by using coated forms of one or more of the offending ingredients (particularly active compounds).
8. Improving product mechanical integrity, since coated products generally are more resistant to mishandling (abrasion, attrition, etc).
9. Modifying drug release, as in enteric-coated, repeat-action and sustained-release products.

Evolution of the Coating Process—Tablet coating is perhaps one of the oldest pharmaceutical processes still in existence and, although a great deal has been written about the materials and methods used, as a process it still often is recognized to be more of an art than a science, a factor which may be responsible for many of the problems that can exist. Historically, the literature cites Rhazes (850–932 AD) as being one of the earliest "tablet coaters," having used the mucilage of psyllium seeds to coat pills that had an offending taste. Subsequently, Avicenna[1] was reported to have used gold and silver for pill coating. Since then, there have been many references to the different materials used in "tablet coating." White[2] mentioned the use of finely divided talc in what was at one time popularly known as "pearl coating," while Kremers and Urdang[3] described the introduction of the gelatin coating of pills by Garot in 1838.

An interesting reference[4] reports the use of waxes to coat poison tablets. These waxes, being insoluble in all parts of the gastrointestinal tract, were intended to prevent accidental poisoning (the contents could be utilized by breaking the tablet prior to use).

While earlier coated products were produced by individuals working in pharmacies, particularly when extemporaneous compounding was the order of the day, that responsibility now has been assumed by the pharmaceutical industry.

The earliest attempts to apply coatings to pills yielded variable results and usually required the handling of single pills. Such pills would have been mounted on a needle or held with a pair of forceps and literally dipped into the coating fluid, a procedure which would have to be repeated more than once to ensure that the pill was coated completely. Subsequently, the pills were held at the end of a suction tube, dipped and then the process repeated for the other side of the pill. Not surprisingly, these techniques often failed to produce a uniformly coated product.[5]

Initially, the first sugar-coated pills seen in the US were imported from France *ca* 1842;[5] while Warner, a Philadelphia pharmacist, became among the first indigenous manufacturers in 1856.[6]

Pharmaceutical pan-coating processes are based on those used in the candy industry, where techniques were highly evolved, even in the Middle Ages. Today, while most coating pans are fabricated from stainless steel, early pans were made from copper, because drying was effected by means of an externally applied heat source. Current thinking, even with conventional pans, is to dry the coated tablets with a supply of heated air, and remove the moisture and dust-laden air from the vicinity of the pan by means of an air-extraction system.

Pan-coating processes underwent little further change until the late 1940s and early 1950s, with the conventional pan being the mainstay of all coating operations up to that time. However, in the last 20 or 30 yr there have been some significant advances made in coating-process technology, mainly as a result of a steady evolution in pan design and its associated ancillary equipment.

Interestingly, in the early years of this development, an entirely new form of technology evolved, that of film coating. Recognizing the deficiencies of the sugar-coating process, advocates of film coating were achieving success by using coating systems involving highly volatile organic solvents. These circumvented the problems associated with the inefficiency in the drying capabilities of conventional equipment, and enabled production quotas to be met with significant reductions in processing times and materials used. The disadvantage of this approach, however, always has been associated with the solvent systems used, which often employed flammable and toxic materials.

The advances that occurred with equipment design, having begun by the development of the Wurster[7] process and continued by the evolution of side-vented pans, have resulted in the gradual emergence of coating processes where drying efficiency can be maximized. Thus, film coating began as a process using inefficient drying equipment, relying on highly volatile coating formulations for success, and evolved into one in which the processing equipment is a major factor in ensuring that rapid drying occurs. Improved drying capabilities have permitted increased use of aqueous film-coating formulations.

Advances in equipment design also have benefited the sugar-coating process, where, because of Current Good Manufacturing Practices (CGMP) and to maintain product uniformity and performance, the trend has been toward using fully automated processes. Nonetheless, film coating tends to dominate as the process of choice for tablet coating.

Pharmaceutical Coating Processes

Basically, there are four major techniques for applying coatings to pharmaceutical solid dosage forms: (1) Sugar Coating, (2) Film Coating, (3) Microencapsulation and (4) Compression Coating.

Although it could be argued that the use of mucilage of psyllium seed, gelatin, etc, as already discussed, was an early form of film coating, *sugar coating* is regarded as the oldest method for tablet coating, and involves the deposition from aqueous solution of coatings based predominantly on sucrose as a raw material. The large quantities of coating material that are applied and the inherent skill often required of the operators combine to result in a long and tedious process.

Film coating, the deposition of a thin polymeric film onto the dosage form from solutions that were initially organic-solvent-based, but which are beginning to rely more and more on water as the prime solvent, have proven to be a popular alternative to sugar coating.

Microencapsulation is a modified form of film coating, differing only in the size of the particles to be coated and the methods by which this is accomplished. This process is based on either mechanical methods such as pan coating, air-suspension techniques, multiorifice centrifugal techniques and modified spray-drying techniques, or physicochemical ones involving coacervation-phase separation, where the material to be coated is suspended in a solution of the polymer. Phase separation is facilitated by the addition of a nonsolvent, incompatible polymer, inorganic salts or by altering the temperature of the system.

Compression coating incorporates the use of modified tableting machines which allow the compaction of a dry coating around the tablet core produced on the same machine. The main advantage of this type of coating is that it eliminates the use of any solvent, whether aqueous or organic in nature. However, this process is mechanically complex and has not proven popular as a method for coating tablets.

Sugar Coating of Compressed Tablets

While the term "sugar" is somewhat generic, and lends itself to describing various raw materials, sugar coating relies mainly on the use of sucrose. The main reason for this is that, based on the techniques involved, it is probably the only material which has enabled smooth, high-quality coatings to be produced, that are essentially dry and tack-free at the end of the process.

While the popularity of sugar coating is waning, this process still retains some popularity, and various companies have invested in complete modernization of the process.

In spite of certain inherent difficulties associated with the sugar-coating process, products which have been expertly sugar coated still remain among the most elegant available.

Since sugar coating is a multistep process, where esthetics of the final coated product is an important goal, it has been, and still is in many companies, highly dependent on the use of skilled manpower. For these reasons, the sugar-coating process is often protracted and tedious. However, processing times have been reduced gradually in the last two decades by the adoption of modern techniques and by the introduction of automation.

The sugar-coating process can be subdivided into six main steps: (1) Sealing, (2) Subcoating, (3) Smoothing, (4) Color Coating, (5) Polishing and (6) Printing.

Sealing—The sealing coat is applied directly to the tablet core for the purpose of separating the tablet ingredients (primarily the drug) and water, which is a major constituent of the coating formulation, in order to assure good product stability. A secondary function is to strengthen the tablet core. Sealing coats usually consist of alcoholic solutions (approximately 10–30% solids) of resins such as shellac, zein, cellulose acetate phthalate or polyvinyl acetate phthalate. Historically, shellac has proven to be the most popular material although it can cause impaired bioavailability due to a change in resin properties on storage. A solution to this problem has been to use a shellac-based formulation containing a measured quantity of polyvinylpyrrolidone (PVP).[8]

The quantities of material applied as a sealing coat will depend obviously on the tablet and batch size. However, another important factor is tablet porosity, since highly porous tablets will tend to soak up the first application of solution, thus preventing it from spreading uniformly across the surface of every tablet in the batch. Thus, one or more further applications of resin solution may be necessary to ensure that the tablet cores are sealed properly.

Since most sealing coats develop a degree of tack (stickiness) at some time during the drying process, it is usual to apply a dusting powder to prevent tablets from sticking together or to the pan. A common material used as a dusting powder is asbestos-free talc. Overzealous use of talc may cause problems, firstly, by imparting a high degree of slip to the tablets, thus preventing them from rolling properly in the pan, and secondly, presenting a surface at the beginning of the subcoating stage which is very difficult to wet, resulting in inadequate subcoat buildup, particularly on the edges. If there is a tendency for either of these problems to occur, one solution is to replace part or all of the talc with some other material such as terra alba, which will form a slightly rougher surface.

If an enteric-coated product is required, additional quantities of the seal-coat solution are applied. In this situation, however, it is preferable to use synthetic polymers such as polyvinyl acetate phthalate or cellulose acetate phthalate.

Subcoating—Subcoating is a critical operation in the sugar-coating process that can have a marked effect on ultimate tablet quality. Sugar coating is a process which often leads to a 50 to 100% weight increase, and it is at the subcoating stage that most of the buildup occurs.

Historically, subcoating has been achieved by the application of a gum-based solution to the sealed tablet cores, and once this has been distributed uniformly throughout the tablet mass, it is followed by a liberal dusting of powder, which serves to reduce tack and facilitate tablet buildup. This procedure of application of gum solution, spreading, dusting and drying is continued until the requisite buildup has been achieved. Thus, in this situation, the subcoating is a sandwich of alternate layers of gum and powder. Some examples of binder solutions are shown in Table I and those of dusting powder formulations in Table II.

Table I—Binder Solution Formulations for Subcoating

	A, % w/w	B, % w/w
Gelatin	3.3	6.0
Gum acacia (powdered)	8.7	8.0
Sucrose	55.3	45.0
Water	to 100.0	to 100.0

Table II—Dusting Powder Formulations for Subcoating

	A, % w/w	B, % w/w
Calcium carbonate	40.0	—
Titanium dioxide	5.0	1.0
Talc (asbestos-free)	25.0	61.0
Sucrose (powdered)	28.0	38.0
Gum acacia (powdered)	2.0	—

Table III—Typical Suspension Subcoating Formulation

	% w/w
Distilled water	25.0
Sucrose	40.0
Calcium carbonate	20.0
Talc (asbestos-free)	12.0
Gum acacia (powdered)	2.0
Titanium dioxide	1.0

This approach has proved to be very effective, particularly where there is difficulty in covering edges, etc. However, if care is not taken, a "lumpy" subcoat will be the result. Also, if the amount of dusting powder applied is not matched to the binding capacity of the gum solution, not only will the ultimate coating be very weak, but also dust will collect in the back of the pan, a factor which may contribute to ultimate roughness.

An alternative approach which has proved popular, particularly when used in conjunction with an automated dosing system, is the application of a suspension subcoat formulation. In such a formulation the powdered materials responsible for coating buildup have been dispersed in a gum-based solution. A typical formulation is shown in Table III. This approach allows the solids loading to be matched more closely to the binding capacity of the base solution, and often permits the less-experienced coater to achieve satisfactory results.

Smoothing—Depending on how successfully the subcoat was applied, it may be necessary to smooth out the tablet surface further prior to application of the color coating. Smoothing usually can be accomplished by the application of a simple syrup solution (approximately 60–70% sugar solids).

Often, the smoothing syrups contain a low percentage of titanium dioxide (1–5%) as an opacifier. This can be particularly useful when the subsequent color-coating formulation uses water-soluble dyes as colorants, since it makes the surface under the color coating more reflective, resulting in a brighter, cleaner final color.

Color Coating—This stage often is the most critical in the successful completion of a sugar-coating process, and involves the multiple application of syrup solutions (60–70% sugar solids) containing the requisite coloring matter. The types of coloring materials used can be divided into two categories: dyes or pigments. The distinction between the two simply is one of solubility in the coating fluid. Since water-soluble dyes behave entirely differently than water-insoluble pigments, the application procedure used in the color coating of tablets will depend on the type of colorant chosen.

When used by a skilled artisan, water-soluble dyes produce the most elegant of sugar-coated tablets, since it is possible to obtain a cleaner, brighter final color. However, since water-soluble dyes are migratory colorants (that is to say, moisture that is removed from the coating on drying will cause migration of the colorant, resulting in a nonuniform appearance), great care must be exercised in their use, particularly when dark shades are required. This can be achieved by applying small quantities of colored syrup that are just sufficient to wet the surface of every tablet in the batch, and then allowing the tablets to dry slowly. It is essential that each application is allowed to dry thoroughly before subsequent applications are made, otherwise moisture may become trapped in the coating and may cause the tablets to "sweat" on standing.

The final color obtained may result from up to 60 individual applications of colored syrup. This factor, combined with the need to dry each application slowly and thoroughly, results in very long processing times (eg, assuming 50 applications are made which take between 15 and 30 min each, the coloring process can extend over a period of up to 25 hr).

Tablet color coating with pigments, as advocated by Tucker *et al*,[9] can present some significant advantages. First of all, since pigment colors are water-insoluble, they present no problems of migration since the colorant remains where it is deposited. In addition, if the pigment is opaque, or is combined with an opacifier such as titanium dioxide, the desired color can be developed much more rapidly, thus resulting in a thinner color coat. Since each color-syrup application now can be dried more rapidly, fewer applications are required and significant reductions can be made in both processing times and costs.

Although pigment-based color coatings are by no means foolproof, they will permit more abuse than a dye color-coating approach, and are more amenable for use by less-skilled coaters. Pharmaceutically acceptable pigments can be classified either as inorganic pigments (eg, titanium dioxide, iron oxides) or certified lakes. Certified lakes are produced from water-soluble dyes by means of a process known as "laking," whereby the dye molecule becomes fixed to a suitable insoluble substrate such as aluminum hydroxide.

Certified lakes, particularly when used in conjunction with an opacifier such as titanium dioxide, provide an excellent means of coloring sugar coatings and permit a wide range of shades to be achieved. However, the incorporation of pigments into the syrup solution is not as easy as with water-soluble dyes, since it is necessary to ensure that the pigment is wetted completely and dispersed uniformly. Thus, the use of pigment color concentrates, which are commercially available, usually is beneficial.

Polishing—Sugar-coated tablets need to be polished in order to achieve a final gloss. Polishing is achieved by applying mixtures of waxes (beeswax, carnauba wax, candelila wax or hard paraffin wax) to the tablets in a polishing pan. Such wax mixtures may be applied as powders or as dispersions in various organic solvents.

Printing—In order to identify sugar-coated tablets (in addition to shape, size and color) often it is necessary to print them, either before or after polishing, using pharmaceutical branding inks, by means of the process of *offset rotogravure*.

Sugar-Coating Problems—Various problems may be encountered during the sugar coating of tablets. It must be remembered that any process in which tablets are kept tumbling constantly can present difficulties if the tablets are not strong enough to withstand the applied stress. Tablets which are too soft, or have a tendency to laminate, may break up and the fragments adhere to the surface of otherwise good tablets.

Sugar-coating pans exhibit inherently poor mixing characteristics. If care is not exercised during the application of the various coating fluids, nonuniform distribution of coating material can occur, resulting in an unacceptable range of sizes of finished tablets within the batch.

Overzealous use of dusting powders, particularly during the subcoating stage, may result in a coating being formed in which the quantity of fillers exceeds the capacity of the binder in the formulation, creating soft coatings or those with increased tendency to crack.

Irregularities in appearance are not uncommon, and occur either as the result of color migration during drying when water-soluble dyes are used, or of "washing back" when overdosing of colored syrups causes the previously dried coating layers to be redissolved. Rough tablet surfaces will produce a "marbled" appearance during polishing, since wax buildup occurs in the small depressions in the tablet surface.

Film Coating of Solid Dosage Forms

Film coating involves the deposition of a thin, but uniform, film onto the surface of the substrate. Unlike sugar coating, the flexibility afforded in film coating allows additional substrates, other than just compressed tablets, to be considered (eg, powder, granules, nonpareils, capsules). Coatings essentially are applied continuously to a moving bed of material, usually by means of a spray technique, although manual application procedures have been used.

Historically, film coating was introduced in the early 1950s in order to combat the shortcomings of the then predominant sugar-coating process. Film coating has proved successful as a result of the many advantages offered, including:

1. Minimal weight increase (typically 2–3% of tablet core weight).
2. Significant reduction in processing times.
3. Increased process efficiency and output.
4. Increased flexibility in formulations.
5. Improved resistance to chipping of the coating.

The major process advantages resulted from the greater volatility of the organic solvents used. However, the use of such organic solvents has created many potential problems, including:

1. Flammability hazards.
2. Toxicity hazards.
3. Concerns over environmental pollution.
4. Cost (either relating to minimizing items 1–3, or to the cost of the solvents themselves).

However, since the initial introduction of film coating, significant advances have been made in process technology and equipment design. The emphasis has changed from needing highly volatile organic solvents (to achieve rapid drying), to attaining the same ultimate effect by designing equipment to have more efficient drying characteristics.

Thus, there has been a transition from conventional pans to side-vented pans and fluid-bed equipment, and consequently from the problematic organic solvent-based process to an aqueous one.

Film Coating Raw Materials—The major components in any film-coating formulation consist of a polymer, plasticizer, colorant and solvent (or vehicle).

Ideal properties for the polymer include solubility in a wide range of solvent systems to promote flexibility in formulation, an ability to produce coatings which have suitable mechanical properties and the appropriate solubility in gastrointestinal fluids such that drug bioavailability is not compromised.

Cellulose ethers are the preferred polymers in film coating, particularly hydroxypropyl methylcellulose. Suitable substitutes are hydroxypropyl cellulose, which may produce slightly tackier coatings, and methylcellulose, although this has been reported to retard drug dissolution.[10] Alternatives to the cellulose ethers are certain acrylics, such as methacrylate and methyl methacrylate copolymers.

Most polymers are employed as solutions in either aqueous or organic solvent-based systems. Alternative systems employ aqueous dispersions of water-insoluble polymers (eg ethylcellulose) in combination with an aqueous solution of, for example, hydroxypropyl methylcellulose.

An additional factor to be considered in the selection of polymers concerns the various molecular-weight grades available for each type. Molecular weight may have an important influence on various properties of the coating system and its ultimate performance, such as solution viscosity and mechanical strength and flexibility of the resultant film.

The incorporation of a plasticizer into the formulation improves the flexibility of the coating, reduces the risk of the film cracking and possibly improves adhesion of the film to the substrate. To ensure that these benefits are achieved, the plasticizer must show a high degree of compatibility with the polymer, and a degree of permanence, if the properties of the coating are to be stable on storage. Examples of typical plasticizers include glycerin, propylene glycol, polyethylene glycols, triacetin, acetylated monoglyceride, citrate esters (eg, triethyl citrate) or phthalate esters (eg, diethyl phthalate).

Colorants usually are used to improve the appearance of the product as well as to increase product identification. Additionally, certain physical properties of the coating (eg its performance as a moisture barrier) may be improved. As in the case of sugar coating, colorants can be classified either as water-soluble dyes or insoluble pigments.

The use of water-soluble dyes is precluded with organic solvent-based film coating because of the lack of solubility in the solvent system. Thus, the use of pigments, particularly aluminum lakes, provides the most useful means of coloring film-coating systems. Although it may seem obvious to use water-soluble dyes in aqueous formulations, the use of pigments is preferred, since:

1. They are unlikely to interfere with bioavailability[11] as do some water-soluble dyes.
2. They help to reduce the permeability of the coating to moisture.[12]
3. They serve as bulking agents to increase the overall solids content in the coating dispersion.

The major solvents used in film coating typically belong to one of these classes: alcohols, ketones, esters, chlorinated hydrocarbons and water. Solvents serve to perform an important function in the film-coating process, since they aid in the application of the coating to the surface of the substrate. Good interaction between solvent and polymer is necessary to ensure that optimal film properties are obtained when the coating dries. This initial interaction between solvent and polymer will yield maximum polymer-chain extension, producing films having the greatest cohesive strength and, thus, the best mechanical properties. An important function of the solvent systems also is to assure a controlled deposition of the polymer onto the surface of the substrate if a coherent and adherent film coat is to be obtained.

Although it is very difficult to give typical examples of film-coating formulations, since these will depend on the properties of the materials used, such formulations usually are based on 5–15% (*w/w*) coating solids in the requisite vehicle (with the higher concentration range preferred for aqueous formulations), of which 60–70% is polymer, 6–7% is plasticizer and 20–30% is pigment.

Modified-Release Film Coatings

Film coatings can be applied to pharmaceutical products in order to modify drug release. One form of coating is used to prevent the release of drugs in, or protect drugs from the effects of, the gastric environment. Such a coating commonly is called an *enteric* coating. Other types of coatings, often called *sustained-* or *controlled-release* coatings, primarily are used to extend the release of a drug over a long period of time.

Enteric Coatings—Enteric coatings are those which remain intact in the stomach, but will dissolve and release the contents of the dosage form once it reaches the small intestine. The purpose of an enteric coating is to delay the release of drugs which are inactivated by the stomach contents, (eg, pancreatin, erythromycin) or may cause nausea or bleeding by irritating the gastric mucosa (eg, aspirin, steroids). In addition, such coatings can be used to give a simple repeat-action effect where additional drug that has been applied over the enteric coat is released in the stomach, while the remainder, being protected by the coating, is released further down the gastrointestinal tract.

The action of enteric coatings results from a difference in composition of the respective gastric and intestinal environments in regard to pH and enzymatic properties. Although there have been repeated attempts to produce coatings which are subject to intestinal enzyme breakdown, this approach is not popular since enzymatic decomposition of the film is rather slow. Thus, most currently used enteric coatings are those which remain undissociated in the low pH environment of the stomach, but readily ionize when the pH rises to about 4 or 5. The most effective enteric polymers are polyacids having a pK_a of 3 to 5.

Historically, the earliest enteric coatings used formalin-treated gelatin, but this was unreliable since the polymerization of gelatin could not be controlled accurately, and often resulted in failure to release the drug, even in the lower intestinal tract. Another early candidate was shellac, but again the main disadvantage resulted from further polymerization that occurred on storage, often resulting in failure to release the active contents. Although the pharmaceutical literature has contained references to many potentially suitable polymers, only three or four remain in use.

The most extensively used polymer is cellulose acetate phthalate (CAP) which is capable of functioning effectively as an enteric coating. However, a pH greater than 6 usually is required for solubility and thus a delay in drug release may ensue. It also is relatively permeable to moisture and gastric fluid compared to most enteric polymers. Thus it is susceptible to hydrolytic decomposition where phthalic and acetic acids are split off, resulting in a change in polymeric, and therefore enteric, properties. Another useful polymer is polyvinyl acetate phthalate (PVAP) which is less permeable to moisture and gastric fluid, more stable to hydrolysis and able to ionize at a lower pH, resulting in earlier release of actives in the duodenum.

A more recently available polymer is hydroxypropyl methylcellulose phthalate. This has similar stability to PVAP and dissociates in the same pH range. A final example of currently used polymers are those based on methacrylic acid—methacrylic acid ester copolymers with acidic ionizable groups. They have been reported to suffer from the disadvantage of having delayed breakdown even at relatively high pH.[13]

Various systems recently have been introduced that allow each of these enteric polymers to be applied as aqueous dispersions, thus facilitating the use of aqueous film-coating technology for the enteric coating of pharmaceutical dosage forms.

Sustained-Release Coatings—The concept of sustained release formulations was developed in order to eliminate the need for multiple dosage regimens, particularly for those drugs requiring reasonably constant blood levels over a long period of time. In addition, it also has been adopted for those drugs which need to be administered in high doses, but where too rapid a release is likely to cause undesirable side effects (eg, the ulceration that occurs when potassium chloride is released rapidly in the gastrointestinal tract).

Formulation methods used to obtain the desired drug availability rate from sustained-action dosage forms include:

1. Increasing the particle size of the drug.
2. Embedding the drug in a matrix.
3. Coating the drug or dosage form containing the drug.
4. Forming complexes of the drug with materials such as ion-exchange resins.

Only those methods which involve some form of coating fall within the scope of this chapter.

Materials which have been found suitable for producing sustained-release coatings include:

1. Mixtures of waxes (beeswax, carnauba wax, etc) with glyceryl monostearate, stearic acid, palmitic acid, glyceryl monopalmitate and cetyl alcohol. These provide coatings which are dissolved slowly or decomposed in the gastrointestinal tract.
2. Shellac and zein—polymers which remain intact until the pH of gastrointestinal contents becomes less acidic.
3. Ethylcellulose, which provides a membrane around the particle and remains intact throughout the gastrointestinal tract. However, it does permit water to permeate the film, dissolve the drug and diffuse out again.
4. Acrylic resins, which behave similarly to ethylcellulose as a diffusion-controlled drug-release coating material.
5. Cellulose acetate (diacetate and triacetate).
6. Silicone elastomers.

As with an enteric coating, many of the synthetic polymers suitable for sustained-release film coating have been converted into commercially available aqueous polymeric dispersion so that aqueous film-coating technology can be employed.[14]

Various methods have been used to prepare sustained-release products using film-coating techniques. Examples include the application of suitable film coatings to:

1. Dried granules (either irregular or spheronized).
2. Drug-loaded beads (or nonpareils).
3. Drug crystals.
4. Drug/ion-exchange-resin complexes.
5. Tablets.

In the first four examples, the final coated particles can either be filled into two-piece hard-gelatin capsules or compacted into tablets. Additionally, coated drug/ion-exchange-resin complexes may be dispersed in viscous liquids to create liquid suspensions.

A rather unique application of the film-coated, sustained-release tablet is the elementary osmotic pump. In this device, a tablet core (formulated to contain osmotically active ingredients) is film coated with a semipermeable membrane, which is subsequently "pierced" with a laser to create a delivery orifice. On the ingestion of such a device, the infusion of water generates an osmotic pressure within the coated tablet that "pumps" the drug in solution out through the orifice.

With sustained-release products, one must remain aware constantly of the fact that the final dosage forms typically contain drug loadings that are sufficiently high to cause problems if the entire dose is released quickly. This phenomenon, commonly called "dose-dumping," can be avoided only if it is ensured that:

1. The film coating is sound mechanically and will resist rupture on ingestion of the dosage form.
2. Sufficient coating is applied uniformly across the surface of the material that is to be coated.

Film-Coating Problems

As with sugar coating, difficulties may develop during, or subsequent to, the film-coating process. The tablets being coated may not be sufficiently robust, or may have a tendency to *laminate* while being coated. Since film coats are relatively thin, their ability to hide defects is significantly less than with sugar coating. Hence, tablets which have poor resistance to abrasion (ie, they exhibit high friability characteristics) can be problematic, since the imperfections readily may be apparent after coating. It is very important to identify tablets with suspect properties, whether mechanically or performance related (eg, poor dissolution), prior to a coating process, since subsequent recovery or reworking of tablets may be extremely difficult after a coating has been applied.

Various process-related problems can occur during the application of a film coating. One example is *picking*, which is a consequence of the fluid delivery rate exceeding the drying capacity of the process, causing tablets to stick together and subsequently become broken apart. Another example, *orange peel* or *roughness*, is usually the result of premature drying of atomized droplets of solution, or it may be a consequence of spraying too viscous a coating solution such that effective atomization is difficult.

Mottling, or lack of color uniformity, can result from uneven distribution of color in the coating, a problem often related to the use of soluble dyes in aqueous film coating, when color migration can occur, either by evolution of residual solvent in the film, or by migration of plasticizer in which the colorant may be soluble. The use of pigments in the film-coating process minimizes the incidence of this latter objection considerably. However, uneven color also can result from poor pigment dispersion in the coating solution.

Finally, some major problems occur as the result of internal stress that develops within the film as it dries. One example is *cracking*, which occurs when this stress exceeds the tensile strength of the film. Another example is *logo-bridging* (ie, a monogram present in the surface of the tablet core), which occurs when a component of the internal stress is able to overcome the adhesive bonds between the coating and the tablet surface, causing the film to pull away so that legibility of the monogram is lost. An understanding of the properties of the various ingredients used in the film-coating formulation, and how these ingredients interact with one another, can allow the formulator to avoid many of these internal-stress-related problems.[15]

Coating Procedures and Equipment

Coating Pans—Sugar coating historically has involved the ladling of the various coating fluids onto a cascading bed of tablets in a conventional coating pan (Fig 90-1), fitted with a means of supplying drying air to the tablets and an exhaust to remove moisture and dust-laden air from the pan.

Typically, after the requisite volume of liquid has been applied, an appropriate amount of time is allowed for the tablets to mix and permit the liquid to be dispersed fully throughout the batch. To facilitate the uniform transfer of liquid, the tablets often are "stirred" by hand, or in larger pans, by means of a rake, to overcome mixing problems often associated with "dead spots," an inherent problem associated with the use of conventional pans. Finally, tablets are dried by directing an air supply onto the surface of the tablet bed. Thus, sugar coating is somewhat of a sequential process consisting of consecutive cycles of liquid application, mixing and drying.

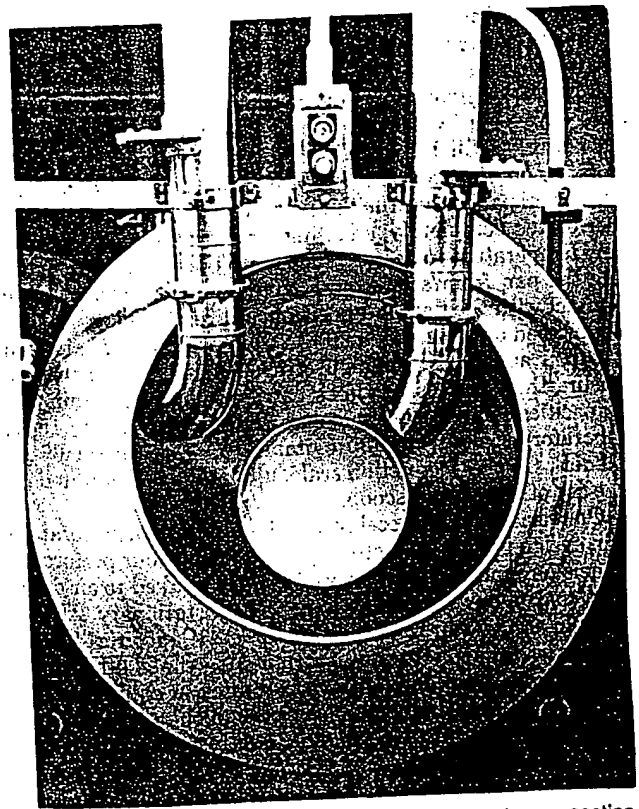


Fig 90-1. Typical equipment setup for conventional sugar coating.

During the early history of film coating, the equipment used was adapted essentially from that already employed for sugar coating. Although ladling of coating liquids during the film-coating process has been practiced, usually the liquid is applied using a spray technique. Spray equipment used are essentially of two types:

1. Airless (or hydraulic) spray, where the coating liquid is pumped under pressure to a spray nozzle with a small orifice, and atomization of the liquid occurs as it expands rapidly on emerging from the nozzle. This is analogous to the effect achieved when one places one's finger over the end of a garden hose.
2. Air spray, whereby liquid which is pumped under little or no pressure to the nozzle is atomized by means of a blast of compressed air that makes contact with the stream of liquid as it passes through the nozzle aperture.

Airless-spray techniques typically are used in large-scale film-coating operations for organic solvents, while air-spray techniques are more effective in either a small-scale laboratory set-up or in the currently popular aqueous film-coating operations.

The use of spray techniques permits the delivery of finely nebulized droplets of a coating solution to the moving tablet mass in such a manner as to ensure uniform coverage while preventing adjacent tablets from adhering together, as the coating solution rapidly dries. Although all the phases that occur during the spray process occur continuously and concurrently, the overall picture can be simplified and represented in the form of several sequential steps, as shown in Fig 90-2. The spray process can be operated either intermittently or continuously.

In the early years of film coating, the lack of adequate drying conditions inside the coating apparatus, together with the preference for using airless coating techniques (and their inherently higher delivery rates) with organic solvent-based formulations on a production scale, gave rise to an intermittent spray procedure. This allowed excess solvent to be removed during the nonspray part of the cycle, and thus reduced the risk of *picking* and the tendency for tablets to stick together. However, in the ensuing years, the improvement in drying capabilities has resulted in a continuous spray procedure being adopted, as this permits a more uniform coating to be developed and results in a shorter, simplified process.

As indicated previously, pan equipment initially was completely conventional in design and, with the exception of the addition of spray-application equipment, was similar to that used in sugar coating. Fortunately, film-coating formulations were based on relatively volatile organic solvents,

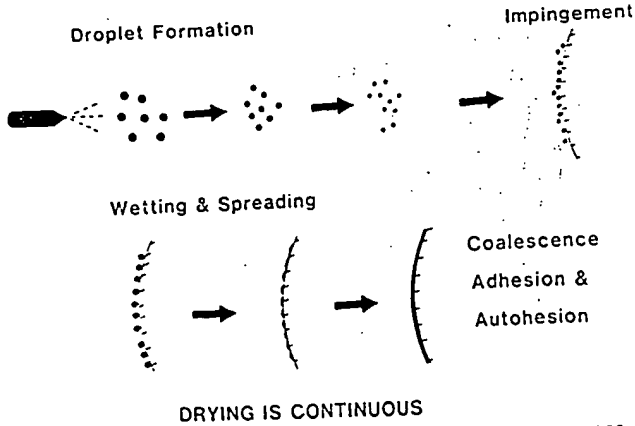


Fig 90-2. Schematic representation of the film-coating process.

which enabled acceptable processing times to be achieved in spite of the relative deficiencies of the air-handling systems. Since the equipment rarely represented a completely enclosed system, it did little to minimize the hazards of using organic solvents. Although conventional pans possessed acceptable properties with regard to mixing of the tablet mass in the sugar-coating process (particularly as this could be augmented by manual stirring of the tablets during processing), they were suited poorly to meet the more rigorous demands of the film-coating process, even when some simple form of baffle system was installed. In spite of these inadequacies, the use of conventional pans has persisted.

The introduction of aqueous film coating in recent years has presented the most serious challenge to conventional equipment. Limitations in both drying and mixing capabilities are likely to increase significantly the processing time and risk to product integrity when aqueous processes are used. The solution to these potential problems has occurred as coating-pan design has evolved and improved.

Although considerable experimentation has taken place with the geometric design of conventional equipment, the most significant change came with the introduction of the Pellegrini coating pan (Fig 90-3), which is somewhat angular and rotates on a horizontal axis. The geometry of the pan, coupled with the fact that there is an integral baffle system, assures much more uniformity in mixing. Additionally, since the services are introduced through the rear opening, the front can either be left free for inspection purposes or simply closed off to yield an enclosed coating system. Although drying air is still applied only to the surfaces of the tablet bed, the other advantages derived from the basic overall design ensure that the Pellegrini pan is suitable more for film coating, including aqueous-based coating solutions, than the conventional equipment previously discussed. Currently, Pellegrini pans are available with capacities ranging from the 10-kg laboratory scale-up to 1000 kg for high-output production.

Considering the relative inefficiencies with equipment in which the majority of drying takes place on the surface of the tablet bed, several attempts have been made to improve air exchange, particularly within the tablet bed. The first to be available on a commercial scale was that developed by Strunck, which, by extending the drying air duct so that it is immersed in the tablet bed, creates a submersed void onto the periphery of which coating solution is applied from a spraygun located in the opening of the supply air duct (Fig 90-4). Exhaust air is taken from the pan in a somewhat conventional manner.

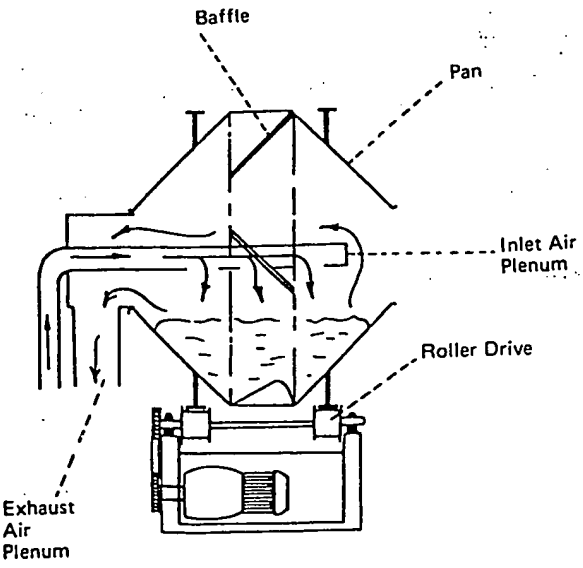


Fig 90-3. Schematic diagram of a Pellegrini coating pan.

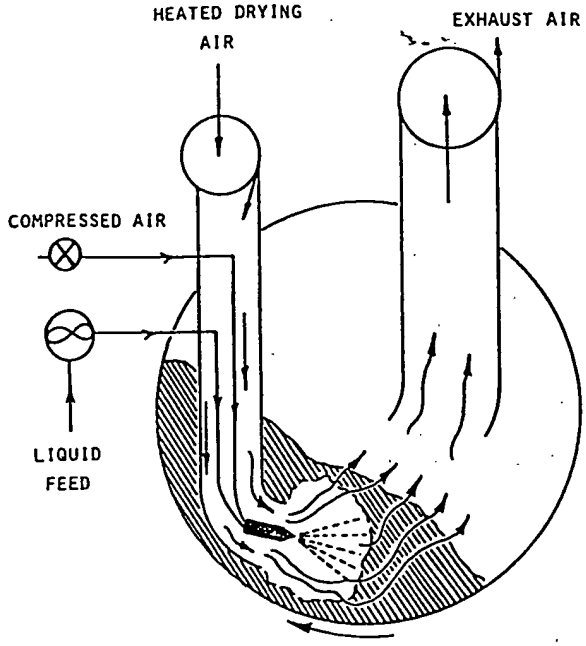


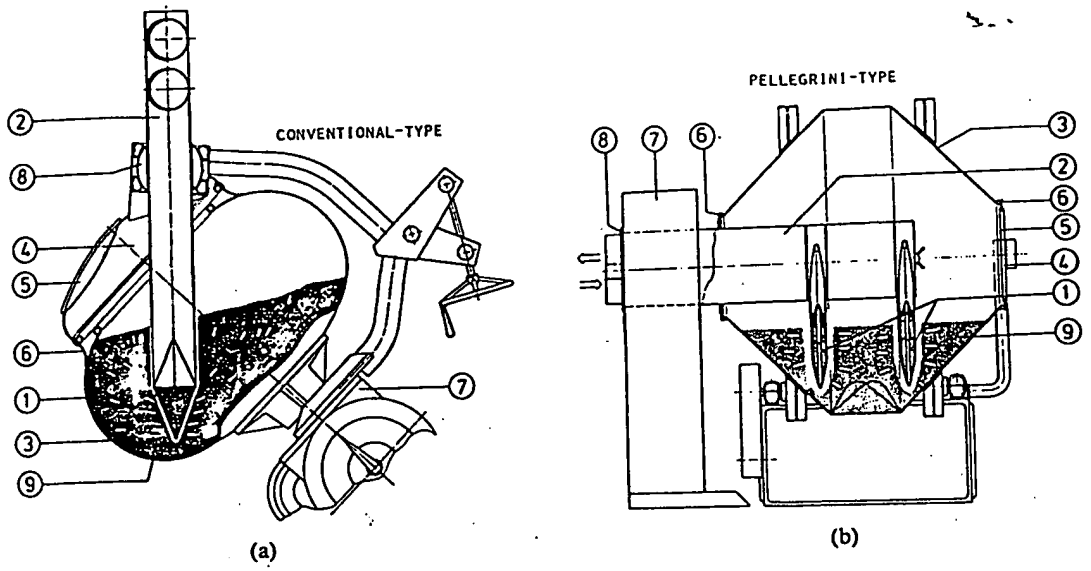
Fig 90-4. Schematic diagram of Strunck immersed-tube coating apparatus.

A second approach, called the Immersion Sword Process, uses a two-chamber system situated in the bed of tablets, enabling heated air to be introduced directly into the tablet bed through perforated air chambers. After interacting with the cascading bed of tablets, the air is drawn into a perforated exhaust air chamber for venting to the outside. This equipment currently is adaptable to both conventional and Pellegrini-type pans (see Fig 90-5). Recently, the manufacturers of the Pellegrini pan introduced a modification to the inlet air supply which permits drying air to be introduced underneath the tablet bed as well as being applied across the surface. A Pellegrini pan so modified is known as a Fast Dry Coater.

A major contribution to film-coating processing technology was made by the introduction of the Accela-Cota, an invention of Eli Lilly & Co. This is also an angular pan rotating on a horizontal axis. The major difference from the Pellegrini pan is that the flat portion of the pan periphery is perforated completely, enabling air of the required volume and temperature to be introduced into the cabinet surrounding the pan from above, and exhausted from a plenum in contact with the pan and positioned directly below the cascading bed of tablets (Fig 90-6). The presence of baffles in the pan augments the high efficiency in air exchange to ensure that processing times can be kept to a minimum. Capacities for this equipment range from the 10- to 15-kg laboratory scale-up to approximately 700 kg for the 66-in. model. On the production scale, unloading is facilitated by the use of the Accela-scoop.

One variant of the Accela-Cota that also uses a perforated-pan design is the Hi-Coater, which contains four perforated panels (around the periphery of the pan) linked to air ducts that continuously make contact with a stationary exhaust plenum as the pan revolves (Fig 90-7). Capacities for the Hi-Coater range from a 300-g (mini) to the 700-kg model HCF-200, with unloading in the production equipment being accomplished by means of a port in the pan periphery enabling discharge to be made directly into a bin placed beneath the machine.

A third type of perforated-pan design is utilized by the



Key: 1. Immersion Sword
2. Coaxial conduit
3. Coating pan
4. Pan cover
5. Clear control cover
6. Silicone seal
7. Stand
8. Coaxial conduit adjustment
9. Coating bed

Fig 90-5. Schematic diagram of the immersed-sword apparatus for use in either (a) a conventional pan or (b) a Pellegrini pan.

Driacoater (Fig 90-8). Unlike the two previous pieces of equipment, heated air is introduced into the back of the cascading bed of tablets by means of ducts, fixed to the outside of the pan. Each duct is connected to a perforated baffle inside the pan and makes intermittent contact with an inlet-air plenum as the pan revolves. This has the effect of partially lifting the tablets and acts as an aid to mixing. Air then is exhausted from the rear of the pan in a similar manner to that in the Pellegrini pan. Thus, drying is countercurrent to the spraying of coating solution. One claim for this equipment, which seems to have been substantiated, is that it tends to be less stressful on the tablets, causing less abrasion. The laboratory model of this equipment holds approximately 5 kg and production models, which are unloaded on reversing the pan via a chute attached to the front of the pan, can handle up to 1000 kg. Finally, more recent introduction of the Glatt Coater (with capacities in the range

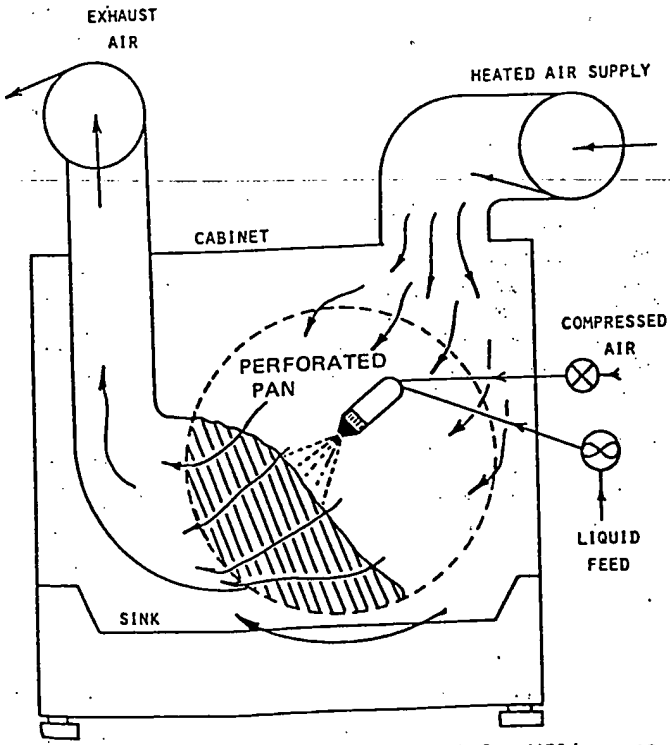


Fig 90-6. Schematic diagram of a 48-in Accela Cota (150-kg capacity).

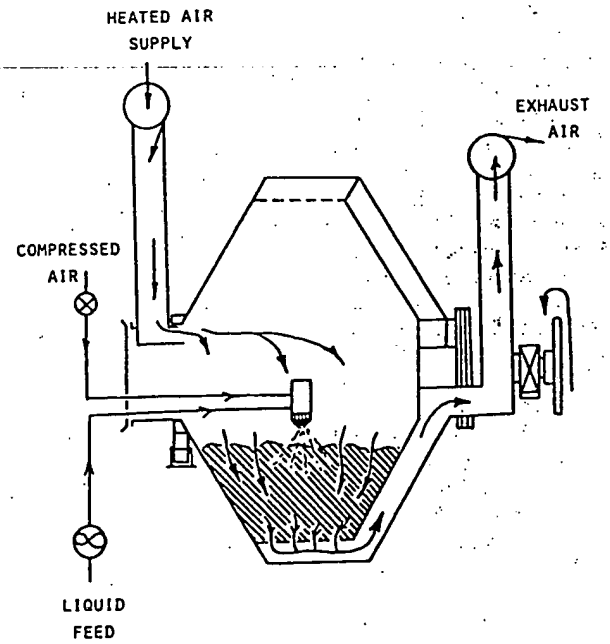


Fig 90-7. Schematic diagram of the Hi-coater.

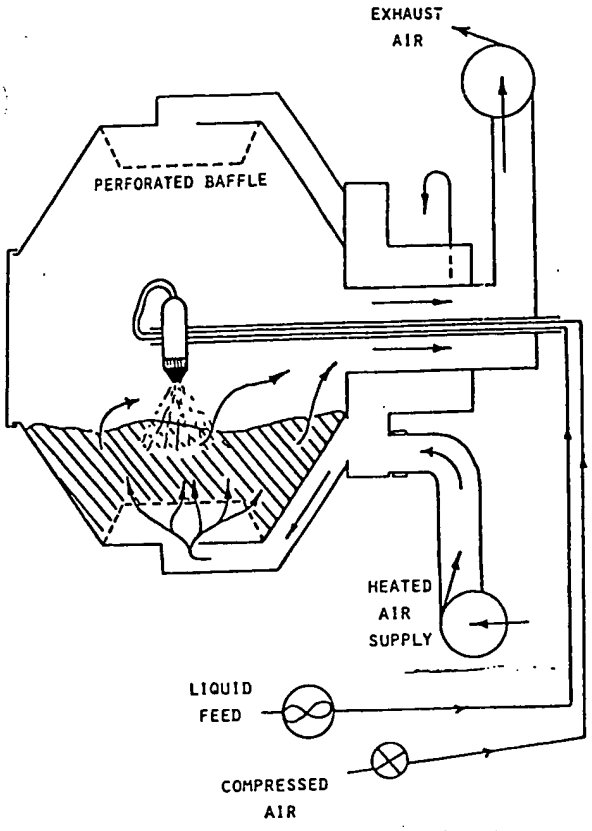


Fig 90-8. Schematic diagram of the Driacoater.

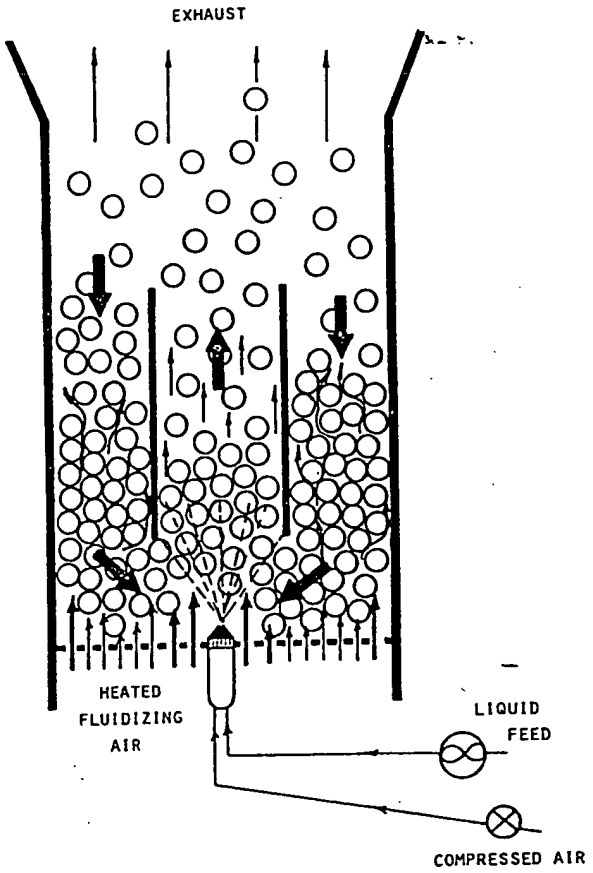


Fig 90-9. Schematic diagram of the Wurster fluidized-bed coater. Perforations in the air-distribution plate are designed to control direction of particle movement.

of 25 to 1000 kg) completes the list of coating-pan types that maximize drying efficiency through perforated-pan design.

Because of a growing requirement for coating drug dosage materials smaller in size than conventional tablets (eg, granules and nonpareils), many of the manufacturers of perforated pans offer suitable equipment modifications to facilitate this.

Although the evolution that has taken place in coating-pan design was done expressly to facilitate film coating, particularly when water is the solvent, the advances in processing technology that are derived are adaptable readily to the sugar-coating process, even though the requirements for in-process drying need not be as rigorous as it is for film coating.

Fluidized-Bed Coating Equipment—Many exponents of this type of equipment will argue, often justifiably so, that it represents the ultimate in drying efficiency since the tablets are supported on a column of moving air allowing for a high area of contact between the drying medium and the product from which solvent must be removed rapidly. The nature of the fluid-bed process, however, essentially restricts its use to film coating. Tablets film coated by the fluidized-bed method often are more glossy, mainly because the coating solution impinges upon them before much solvent loss has occurred. Limitations of fluid-bed equipment in tablet coating occur as the result of the rigorous treatment that tablets receive, causing greater potential for tablet damage. Fluid-bed coating equipment is, however, becoming preeminent for the purpose of applying modified-release film coatings to particulates.

The earliest fluid-bed coating equipment was based on the Wurster design, (Fig 90-9). A moving bed of tablets continuously passes up the central column and, as a result of the effect of an expansion chamber at the top which reduces air velocity, the tablets drop back to the bottom between the walls of the inner and outer chamber. The concept of the equipment is based on a single spraygun situated in the center of an air-distribution plate. The geometric proportions of the inner and outer columns are such that a continuously moving column of tablets passes through the spray path with every tablet capturing some of the coating and, at the same time, ensuring that little or no solution reaches the wall of the inner column.

While laboratory models usually are equipped with either 6- or 12-in-diameter outer chambers (having capacities in the range of 1–2 kg and 10–15 kg, respectively), production models usually are based on an 18-in chamber diameter. Any attempt to increase the diameter while retaining only a single spraygun usually results in some tablets passing through the spray zone without receiving any coating. Consequently, large models use multiples of the 18-in concept; for example, the 32-in model has three inner-coating partitions and sprayguns, while the 46-in model has seven, all based on the 18-in model geometry, allowing for capacities up to approximately 400 kg.

The design of currently available fluid-bed equipment permits a lot of versatility in processing. Equipment available from several manufacturers (*Glatt*, *Aeromatic* and *Vector/Freund*) is designed on the multiple-insert principle, which permits various types of unit processes to be undertaken, including:

1. Wurster coating.
2. Rotor granulation (to produce spheroids) and coating.
3. Fluid-bed granulation.
4. Fluid-bed drying.

Each of these processes can be performed by removing one type of insert and replacing it with another.

A rather innovative approach to fluid-bed coating occurred recently with the introduction of the Kugel coater.[16]

Potential for Totally Automated Coating Systems—During the last few decades, the industry has witnessed a general transition from manually operated sugar-coating procedures, requiring total operator involvement, to film-coating ones in which operator intervention is infrequent. Increasing familiarity with, and understanding of, tablet coating as a unit process, and a desire to ensure compliance with GMPs, ultimately have increased the desire for assuring uniformity to design specifications of every batch of product made. Obviously, this is difficult for any process where the idiosyncracies of individual operators must have a significant impact.

Total automation of the process can provide a solution to these problems. This involves developing a process where all the important variables and requisite constraints are predetermined. These then can be translated into a form such that ultimate control and monitoring of the various process parameters can be maintained either by a microprocessor or central computer system. However, the system only will be as good as those peripheral devices used to detect various process conditions such as air flow, temperature, humidity, application volumes, delivery rates, etc.

Since a sugar-coating process always has been highly operator-dependent, removal of much of the operator intervention could be achieved by automation. Automation has, however, been complex because of the various sequences that occur and the variety of coating fluids used in a single process. That it has been accomplished is evidenced by the number of commercially available systems which have been introduced.[17] The technology for automated control of both sugar- and film-coating processes has become very refined, and most major equipment suppliers are able to offer a coating process that is automated to various degrees (depending on end-user preferences).

Quality Control of Coated Tablets

The most important aspects of coated tablets which must be assessed from a quality-control standpoint are appearance characteristics and drug availability. From the appearance standpoint, coated tablets must be shown to conform, where applicable, to some color standard, otherwise the dispenser and the consumer may assume that differences have occurred from previous lots, signifying a changed or substandard product. In addition, because of the physical abuse that tablets, both in their uncoated and coated forms, receive during the coating process, it is essential to check for defects such as chipped edges, picking, etc, and ensure they do not exceed predetermined limits.

Often, in order to identify the products, coated tablets may be imprinted (particularly with sugar-coated tablets) or bear a monogram (commonly seen with tablets that are film-coated). The clarity and quality of such identifying features must be assessed. The failure of a batch of coated tablets to comply with such preset standards may result in 100% inspection being required or the need for the batch to be reworked.

Batch to batch reproducibility for drug availability is of paramount importance, consequently each batch of product should be submitted to some meaningful test such as a dissolution test. Depending on the characteristics of the tablet core to be coated, tablet coatings can modify the drug-release profile, even when not intended (unlike the case of enteric- or controlled-release products). Since this behavior may vary with each batch coated (being dependent, for example, on differences in processing conditions or variability in raw materials used), it is essential that this parameter should be assessed, particularly in products that are typically borderline (refer to Chapter 89).

Stability Testing of Coated Products

The stability-testing program for coated products will vary depending on the dosage form and its composition. Many stability-testing programs are based on studies which have disclosed the conditions a product may encounter prior to end use. Such conditions usually are referred to as normal and include ranges in temperature, humidity, light and handling conditions.

Limits of acceptability are established for each product for qualities such as color, appearance, availability of drug for absorption and drug content. The time over which the product retains specified properties, when tested at normal conditions, may be defined as the *shelf life*. The container for the product may be designed to improve the shelf life. For example, if the color in the coating is light-sensitive, the product may be packaged in an amber bottle and/or protected from light by using a paper carton. When the coating is friable, resilient material such as cotton may be incorporated in both the top and bottom of the container, and if the product is affected adversely by moisture, a moisture-resistant closure may be used and/or a desiccant may be placed in the package. The shelf life of the product is determined in the commercial package tested under normal conditions.

The stability of the product also may be tested under exaggerated conditions. This usually is done for the purpose of accelerating changes so that an extrapolation can be made early, concerning the shelf life of the product. Although useful, highly exaggerated conditions of storage can supply misleading data for coated dosage forms. Any change in drug release from the dosage form is measured *in vitro*, but an *in vivo* measurement should be used to confirm that drug availability remains within specified limits over its stated shelf life. This confirmation can be obtained by testing the product initially for *in vivo* availability and then repeating at intervals during storage at normal conditions for its estimated shelf life (or longer).

Stability tests usually are conducted on a product at the time of development, during the pilot phase and on representative lots of the commercial product. Stability testing must continue for the commercial product as long as it remains on the market because subtle changes in a manufacturing process and/or a raw material can have an impact on the shelf life of a product.

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Pharmacokinetics of Paracetamol (Acetaminophen) after Intravenous and Oral Administration

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Summary. Plasma paracetamol concentrations were measured in 6 volunteers after single intravenous (1000 mg) and oral (500 mg, 1000 mg and 2000 mg) doses of the drug. Paracetamol levels declined multiphasically with a mean clearance after intravenous administration of 352 ± 40 ml/min. A two-compartment open model appeared to describe the decline adequately. Comparison of the areas under the plasma concentration-time curves (AUC) indicated that oral bioavailability increased from 0.63 ± 0.02 after 500 mg, to 0.89 ± 0.04 and 0.87 ± 0.08 after 1000 mg and 2000 mg, respectively. As a consequence of the incomplete bioavailability of paracetamol, as well as its multicompartmental distribution, accurate estimates of its distribution volume and clearance cannot be obtained if the drug is given orally. However, an estimate of its total plasma clearance may be derived from the AUC after a 500 mg oral dose.

Key words: Paracetamol, Acetaminophen, pharmacokinetics, first-pass elimination, intravenous administration

Paracetamol (N-acetyl-paraminophenol; acetaminophen) is a widely used non-narcotic analgesic. It is eliminated in the urine predominantly as sulphate and glucuronide conjugates (Cummings et al., 1967), and has therefore been used as a "model" substrate for examining conjugation mechanisms in man (Triggs et al., 1975; Shively & Vesell, 1975). However, although its absorption characteristics have been studied extensively in man (Heading et al., 1973), its distribution and elimination kinetics have been inadequately investigated. We have therefore examined and compared these aspects of paracetamol kinetics following both intravenous and oral administration to healthy volunteers.

Methods and Materials

Six healthy male subjects consented to participate in the study which had received prior approval from the local ethical committee. All the subjects denied having consumed any drug in the four weeks before the start of the project. On separate occasions (at least one week apart) each volunteer received 1000 mg paracetamol intravenously (as a 20 mg/ml solution over 5 minutes), and 500 mg, 1000 mg, and 2000 mg orally as tablets (Panadol®). Venous blood was withdrawn from an indwelling cannula at 0, 15, 30, 45, 60, 90, 120, 180, 240, 300 and 360 minutes after the intravenous injection (timed from the mid-point of the 5-minute infusion) and at 0, 30, 60, 90, 120, 180, 240, 300 and 360 minutes after oral dosing. Heparinised plasma was stored at −20° C before analysis in duplicate by gas chromatography (Prescott, 1971).

The decline in plasma paracetamol concentration (C_t) after intravenous administration appeared to be bi-exponential: −

$$C_t = Ae^{-\alpha t} + Be^{-\beta t} \quad (1)$$

and the data was interpreted in the form of a two-compartment open model (Riggs, 1963). The volumes V_1 (central, sampling compartment) and V_2 (peripheral compartment), the intercompartmental rate constants k_{12} and k_{21}, and the true elimination rate constant k_{13} were derived from the hybrid terms A, B, α and β of equation 1 (Riggs, 1963). These hybrid terms were calculated by least-squares regression analysis and the method of residuals. The area under the plasma concentration time curve (AUC) was determined by the trapezoidal rule, and extrapolated to infinity: the latter never exceeded 15% of the total AUC. The terminal (3−6 h) mono-exponential decline in plasma paracetamol concentration after oral dosing was used to calculate the oral half-life of the drug ($T^1/_2$). Bioavailability (F) was determined: −

$$F = \frac{\text{AUC oral}}{\text{AUC i.v.}} \times \frac{\text{Dose i.v.}}{\text{Dose oral}} \quad (2)$$

and plasma clearance ($\dot{V}p$) as (Riggs, 1963): –

$$\dot{V}p = \frac{\text{Dose i.v.}}{\text{AUC i.v.}} \quad (3)$$

Results

Intravenous Administration

The decline of plasma paracetamol concentrations in our subjects is shown in Figure 1. An initial rapid fall over the first 1.5 h was followed by a mono-exponential decline over the remaining 4.5 h of observation and could be described by the equation (see Table 1): –

$$C_t = 13.8 \cdot e^{-2.55t} + 13.0 \cdot e^{-0.28t} \quad (4)$$

The half-life ($T^1/_{2\alpha}$) of the first exponential ranged from 0.15 to 0.53 hrs (mean = 0.32 h) and that of the second exponential $T^1/_{2\beta}$) ranged from 2.24 to 3.30 h (mean = 2.50 h).

The compartmental volumes and intercompartmental rate constants are shown in Table 1. There was little interindividual variability in apparent distribution volume and, as expected from the multiphasic decline in concentration, β was observed to be a poor estimate of k_{13}. Plasma clearance (equation 3) ranged from 264 to 505 ml/min (352 ± 40 ml/min, mean ± S.E.).

Oral Administration

The mean plasma concentrations of paracetamol after 500 mg, 1000 mg and 2000 mg doses are shown in Figure 2. Plasma concentrations reached a maximum at 0.5 to 1.0 hrs after dosing with 500 mg and 1000 mg, but continued to rise for 2 h after 2000 mg. The decline in plasma concentration appeared to be biphasic with a terminal mono-exponential decay after 3 hours. The $T^1/_2$ oral was therefore calculated from the concentrations observed at 3, 4, 5, and 6 hours after dosing (see Table 2). No difference in $T^1/_2$ oral was observed between doses, and no difference was found between $T^1/_{2\beta}$ after intravenous and oral dosing.

Oral bioavailability (equation 2) was incomplete at all dose levels (see Table 2) and was significantly ($P < 0.05$) less after 500 mg than after 1000 mg or 2000 mg.

Discussion

Our study indicates that paracetamol kinetics are more complicated than previously supposed. The decline in plasma concentration after intravenous injection is multiphasic and incompatible with a one-compartment open model. Although we have interpreted our data according to a two-compartment open model this cannot be regarded as a unique solution: not only might more frequent early sampling have revealed a third exponential component to the decline in drug concentration, but "central" compartment sampling is also limited in its ability to recognise small "deep" compartments (Rawlins et al., 1976). The multiphasic decline of plasma paracetamol levels was also observed after oral dosing with 500 mg and 1000 mg, but not after 2000 mg – presumably because of the slower absorption rate at this dose level (see Figure 2).

The slope of the terminal (β) exponential decline in concentration ($0.28 \pm 0.02\,h^{-1}$) was observed to be a gross underestimate of the elimination rate (k_{13}) constant (0.51 ± 0.06 hours^{-1}). There was no significant correlation between $\dot{V}p$ and either β or k_{13} ($r = 0.803$, $0.1 > P > 0.05$; $r = 0.153$, $P < 0.1$, respectively). Estimates of the rate of paracetamol elimination can only therefore be obtained by measurement of $\dot{V}p$. Incomplete bioavailability was observed at all dose levels (see Table 2). Since the absorption of paracetamol from the gastrointestinal tract is virtually complete, "first-pass" elimination by the liver or gut wall is likely to account for this. Such an explanation would be compatible with the observation that bioavailiability was significantly less after 500 mg, than after 1000 mg or 2000 mg orally. The absence of significant differences in $T^1/_{2\beta}$ between the three oral doses would not support a hypothesis of dose-dependent elimination.

These observations have important implications for the use of paracetafnol as a "model" substrate. First, $T^1/_{2\beta}$ (oral or intravenous) is a poor estimate of the elimination rate of the drug in man. Second, dose-dependent "first-pass" elimination of paracetamol means that estimates of distribution volume and clearance after oral dosing are unacceptable. However, a significant correlation was found between the AUC after an oral dose of 500 mg, and $\dot{V}p$ calculated from the intravenous studies ($r = -0.876$; $P < 0.05$): –

$$\dot{V}p = 728 - 23\,(\text{AUC}) \quad (5)$$

No significant ($P > 0.05$) correlation was observed between $\dot{V}p$, and the AUC after oral dosing with 1000 mg ($r = -0.527$) and 2000 mg ($r = -0.734$) – probably because of the greater variance in bioavailability at these doses (see Table 2). If paracetamol elimination is therefore to be studied quantitatively,

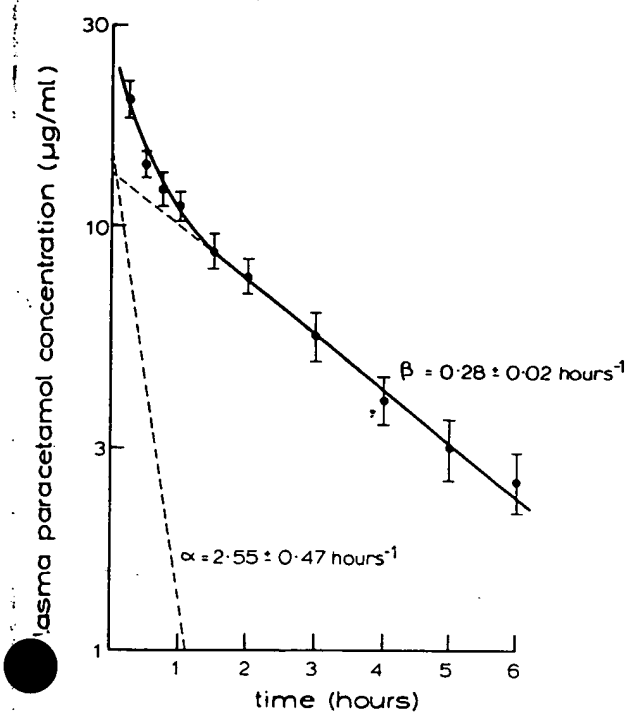

Fig. 1. Plasma concentrations of paracetamol (logarithmic scale) ± S.E.M. after the intravenous administration of 1000 mg to six volunteers. The solid line represents the least-squares regression equation: –

$C_t = 13.8 \cdot e^{-2.55t} + 13.0 \cdot e^{-0.28t}$

The dashed lines represent the fast and slow exponential slopes

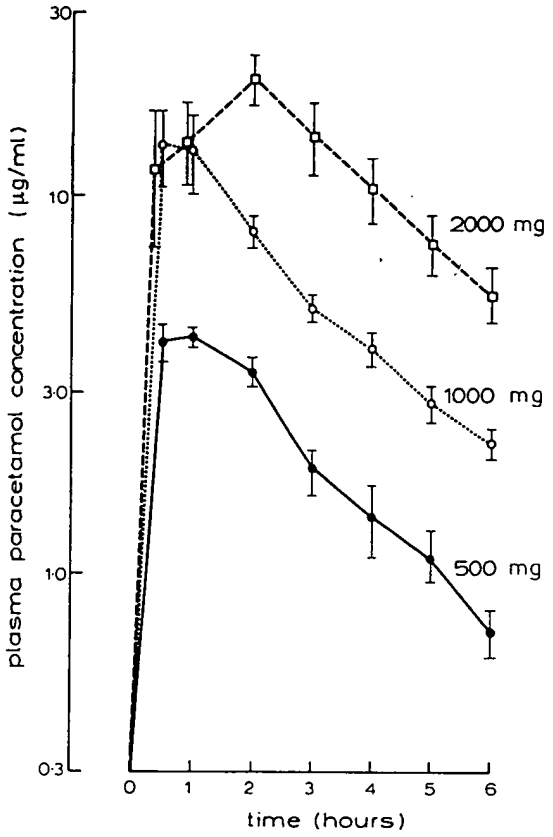

Fig. 2. Plasma concentrations of paracetamol (logarithmic scale) ± S.E.M. after the oral administration of 500 mg, 1000 mg and 2000 mg to six volunteers

Table 1. Pharmacokinetic variables calculated after the intravenous administration of 1000 mg paracetamol (mean ± S.E.M.)

A	= 13.8 ± 2.5 µg/ml
α	= 2.55 ± 0.47 hrs^{-1}
B	= 13.0 ± 1.0 µg/ml
β	= 0.28 ± 0.02 hrs^{-1}
AUC	= 50.5 ± 5.7 µg/ml · h
$\dot{V}p$	= 352 ± 40 ml/min
V_1	= 0.60 ± 0.07 l/kg
V_2	= 0.35 ± 0.02 l/kg
k_{12}	= 0.95 ± 0.27 hrs^{-1}
k_{21}	= 1.41 ± 0.18 hrs^{-1}
k_{13}	= 0.51 ± 0.06 hrs^{-1}

K_{10}

Table 2. Pharmacokinetic constants calculated after oral administration of paracetamol (mean ± S.E.M.)

Dose (mg)	Area under plasma concentration-time curve (µg/ml · hour)	Apparent half-life (hrs)	Bioavailability
500	15.6 ± 3.4	2.79 ± 0.35	0.63 ± 0.02
1000	44.0 ± 3.7	2.68 ± 0.17	0.89 ± 0.04
2000	87.6 ± 12.6	2.31 ± 0.18	0.87 ± 0.08

or to be used as a "model" substrate, clearance should either be measured directly (after intravenous administration) or inferred from an estimate of the AUC after 500 mg orally. In our study doses were not adjusted for body size and the subjects' weights ranged from 65–72 kg. It would therefore be advantageous for studies utilizing equation 5 to administer the drug in a dose of 7 mg/kg body weight.

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New Methods of Drug Delivery

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Conventional forms of drug administration generally rely on pills, eye drops, ointments, and intravenous solutions. Recently, a number of novel drug delivery approaches have been developed. These approaches include drug modification by chemical means, drug entrapment in small vesicles that are injected into the bloodstream, and drug entrapment within pumps or polymeric materials that are placed in desired bodily compartments (for example, the eye or beneath the skin). These techniques have already led to delivery systems that improve human health, and continued research may revolutionize the way many drugs are delivered.

IN THE LAST FEW YEARS, WE HAVE WITNESSED AN EXPLOSION in research aimed at creating new drug delivery systems. This research has been fueled by several developments. (i) Many drugs, both old pharmaceutical products and new molecular entities, can be administered in ways that not only improve safety and efficacy but, in some cases, permit new therapies. (ii) Newer and complex drugs such as proteins are becoming available through genetic engineering; the delivery of these drugs is often more complicated than that of more conventional drugs, necessitating novel delivery systems. (iii) There is an increasing awareness that drug release patterns (continuous versus pulsatile) significantly affect therapeutic responses. (iv) The overall expense to create a pharmaceutical that is a new molecular entity is at least $150 million; the lower cost to improve the delivery of an existing drug is sometimes seen as a better investment. This issue is exacerbated because drug patents expire after 17 years, and a new drug delivery system may permit continued benefits for the company producing it. (v) Advances in materials science and biotechnology are permitting the development of new physical and chemical methods of drug delivery. In this article, some of the methods being studied to deliver drugs are discussed.

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Chemical Modification

A drug may be chemically modified to selectively alter such properties as biodistribution, pharmacokinetics, solubility, or antigenicity. One example is drugs that are designed to cross a normally impermeable barrier. The blood brain barrier, which contains tight endothelial cell junctions and prevents most molecules from entering the central nervous system, has been the target of considerable research. Several experimental approaches have been developed, in which drugs are complexed to agents that enable them to cross this barrier (for example, by rendering the drug more lipophilic or coupling it to a molecule that has a specific transport mechanism) (*1*).

Drugs have also been attached to soluble macromolecules such as proteins, polysaccharides, or synthetic polymers via degradable linkages. This process alters the drug's size and other properties, resulting in different pharmacokinetics and biodistribution. One example involves coupling the antitumor agent neocarzinostatin to styrene–maleic acid copolymers (*2*). When this complex was injected intra-arterially into patients with hepatocellular carcinoma, decreases in α-fetoprotein levels and tumor size were observed. In animals, antitumor agents such as doxorubicin coupled to *N*-(2-hydroxypropyl) methacrylamide copolymers showed radically altered pharmacokinetics, resulting in reduced toxicity. The half-life of the drug in plasma and the drug levels in the tumor were increased while the concentrations in the periphery decreased (*3*).

An exciting approach for "targeting" drugs to specific cells involves linkage of a bioactive agent (drug, radioisotope, or toxin) to a monoclonal antibody. Antibody conjugates are now being studied in the treatment of cancer, septic shock, and acquired immunodeficiency syndrome (AIDS). There are several critical issues in the use of antibodies. With mouse antibodies, anaphylactic reactions frequently occur with repeated administration. Thus, ongoing research is directed toward producing human monoclonal

antibodies or toward making mouse antibodies more human-like through the use of genetic engineering. This problem may be exacerbated for immunotoxins (antibody-toxins) because of the proteinaceous character of the toxin. Thus far, clinical usefulness of immunotoxins has been demonstrated in therapy regimens characterized by rapid pharmacokinetics, such as treatments for lymphoma and graft versus host disease, and extracorporeal treatments such as bone marrow purgings. The powerful killer potential of certain toxins, such as ricin or diphtheria toxin, makes immunotoxins an attractive approach if an appropriate antibody is available that can be internalized by desired cells (*4*). Antibody-radioisotopes act over a greater distance than immunotoxins. One requirement with such complexes is the availability of a suitable chelator that allows a kinetically stable binding of the radioisotope. The degradation of the linker structure between the chelator and antibody is also critical, since nondegradable structures may cause kidney and liver toxicity. Initial clinical results with certain beta-emitters have shown regression of lymphomas. Other critical issues in the use of an antibody are its affinity, specificity, size, and large-scale production; for cancer chemotherapy, tumor characteristics and blood flow are important considerations (*5*).

Polymers, such as polyethylene glycol (PEG), can be attached to drugs to either lengthen their lifetime or alter their immunogenicity. The polymers physically prevent cells and enzymes from attacking the drug. PEG-uricase reduced serum urate levels in patients with hyperuricemia and gout; PEG-asparaginase has been used for patients with leukemia, and PEG–adenosine deaminase has been used for patients with a severe combined immunodeficiency (*6*). Drug longevity and immunogenicity may also be affected by biological approaches, including protein engineering and altering glycosylation patterns.

Vesicles

Vesicles are microparticulates or colloidal carriers composed of substances such as proteins, lipids (for example, liposomes), carbohydrates, or synthetic polymers. Vesicles share some of the advantages of drug-macromolecular conjugates (altered pharmacokinetics and biodistribution) and make possible a potentially higher drug payload. Liposomes, the most widely studied of these vesicles, can be formulated with a variety of lipid compositions and structures and are potentially nontoxic, degradable, and nonimmunogenic. However, many liposomes exhibit poor stability during storage and use. Liposome stability may be improved by increasing the liposomal cholesterol content or synthesizing polymerizable liposomes, but biodegradability may then be diminished (*7*). Engineering issues such as large-scale lipid production and manufacturing of liposomes are also critical to the more widespread use of these vesicles.

In clinical studies, liposomal doxorubicin reduces side effects such as alopecia and nausea associated with the administration of the free drug yet permits a higher maximal tolerated dose and a reduction in cardiac toxicity of 86% (*8*). Liposomal amphotericin B is more effective than the free drug in treating immunocompromised cancer patients with fungal infections (*9*). Methods are also being studied to create liposomes that release more drug in response to specific stimuli such as heat, enzymes, polycations, light, or pH (*10*).

Vesicles may be "targeted" either passively or actively. Passive targeting involves the natural uptake by cells that scavenge foreign microparticulates such as reticuloendothelial cells, which are concentrated in tissues such as the liver or spleen, or circulating monocytes. Thus, liposomes have been used for delivering toxic agents, such as arsenic, to treat liver-specific parasitic diseases (for example, schistosomiasis) in animal models (*11*) with doses 0.1% of those of conventional regimens. Similarly, immunostimulating agents encapsulated in liposomes are taken up by monocytes, which then leads to enhanced killer cell activity. This approach is being tested in certain cancer treatments (*12*). Liposomes can also be used to deliver vaccines (*13*).

Active targeting generally involves placing a charge or recognition sequence (for example, from an antibody) onto the vesicle such that it is more rapidly taken up by certain cell types (such as cancer cells) than others. One difficulty with this approach is that reticuloendothelial cells also scavenge these vesicles. However, recent approaches for altering vesicle compositions, by coating them with surfactants or altering lipid compositions, may reduce the magnitude of this problem (*14*). Vesicles that contain magnetic microparticles have also been used to target drugs to specific locations in animal models via external magnetic fields (*15*).

Controlled Release Systems

Controlled release systems deliver a drug at a predetermined rate for a definite time period. In general, release rates are determined by the design of the system and are nearly independent of environmental conditions, such as pH. These systems can also deliver drugs for long time periods (days to years). Although vesicles or drug macromolecule conjugates may prolong release, optimal control is afforded if the drug is placed in a polymeric material or pump. Controlled release systems differ from older "sustained release" or "slow release" preparations that include complexes (to salts or ion-exchange resins), suspensions, emulsions, slowly dissolving coatings that do not dissolve in the stomach yet do dissolve in the intestine (enteric coatings), and compressed tablets. Generally, sustained-release systems emit drugs in less than a day, and environmental conditions influence release rates, which leads to patient to patient variations.

Controlled release systems provide advantages over conventional drug therapies. For example, after ingestion or injection of standard dosage forms, the blood level of the drug rises, peaks, and then declines. Since each drug has a therapeutic range above which it is toxic and below which it is ineffective, oscillating drug levels may cause alternating periods of ineffectiveness and toxicity. Although sustained release preparations attenuate the peaks and valleys, they do not eliminate them. In contrast, a controlled release preparation maintains the drug in the desired therapeutic range by a single administration. Other potential advantages of controlled release systems include (i) localized delivery of the drug to a particular body compartment, thereby lowering the systemic drug level; (ii) preservation of medications that are rapidly destroyed by the body (this is particularly important for biologically sensitive molecules such as proteins); (iii) reduced need for follow-up care; (iv) increased comfort; and (v) improved compliance.

Pumps are larger and more costly than polymeric systems and require surgery for implantation; however, they offer the advantage of very precise drug control and can release the drug directly into the bloodstream. In addition, some pumps are refillable. Both externally worn and implantable pumps have been developed. In both cases, the driving force is a pressure difference, which results in bulk flow of a drug solution through an orifice.

A common externally worn pressure-driven pump is the miniature syringe pump, in which the drug is delivered at a constant rate by a syringe barrel that moves at a constant velocity; the delivery rate is adjusted by altering either the drug concentration in the syringe or the barrel velocity. An implantable pressure-driven pump has been developed that uses a fluorocarbon propellant as a driving force. In this case, the pump controls a collapsible bellows, which divides the

pump interior into two chambers, one containing the propellant and the other containing the drug solution. At body temperature, the vapor pressure exerted by the propellant forces the drug solution through a filter and flow regulator at a constant rate. Other pressure-driven pumps use piezoelectric disk benders or valves. Release rates can be externally regulated by the use of approaches such as telemetry. Pumps have been used in cancer therapy where a catheter extending from a pump is selectively inserted into a blood vessel feeding an organ such as the liver or brain to increase the delivery rate to the diseased organ while sparing the rest of the body. Pumps have also been used to release insulin, heparin, morphine, and other drugs (*16*).

Polymeric materials generally release drugs by the following mechanisms: (i) diffusion, (ii) chemical reaction, or (iii) solvent activation. There are two types of diffusion-controlled systems: reservoirs (Fig. 1A) and matrices (Fig. 1B). Chemical control is accomplished either by polymer degradation (Fig. 1C) or chemical cleavage of the drug from a polymer (Fig. 1D). Solvent activation involves either swelling of the polymer (Fig. 1E) or osmotic effects (Fig. 1, F and G).

One of the first clinically used controlled release polymer systems was the Ocusert, a reservoir system designed to improve therapy for glaucoma, one of the world's leading causes of blindness. The conventional treatment involved the use of pilocarpine eye drops (which reduce intraocular pressure) four times a day. The eye drops often caused side effects, and patient compliance was sometimes poor. The Ocusert delivers pilocarpine (20 or 40 μg/hour) continuously for 1 week and controls intraocular pressure with less drug and fewer side effects. It is placed in the lower eyelid's conjunctival cul-de-sac, where it floats in the tear film. Despite its advantages, the Ocusert never achieved widespread use, initially because of its expense and poor acceptance by older patients who were reluctant to adjust to this system and later because of the introduction of timolol, a drug that requires only two applications per day.

The use of polymers to deliver contraceptive steroids has been widely studied. Four types of systems have been examined: (i) subdermal reservoir implants composed of nondegradable polymers that release drug for over 5 years (for example, the Norplant); these systems, based on a seminal study of diffusion through silicone rubber (*17*), are approved for use in 15 countries; (ii) subdermal implants or injectable microspheres composed of degradable materials, such as lactic acid–glycolic acid copolymers, polycaprolactones, or cholesterol; (iii) steroid-releasing intrauterine devices, such as the Progestasert, an ethylene–vinyl acetate copolymer reservoir that contains a 3-day supply (38 mg) of the amount of progesterone normally taken orally, but which, since it delivers progesterone to its

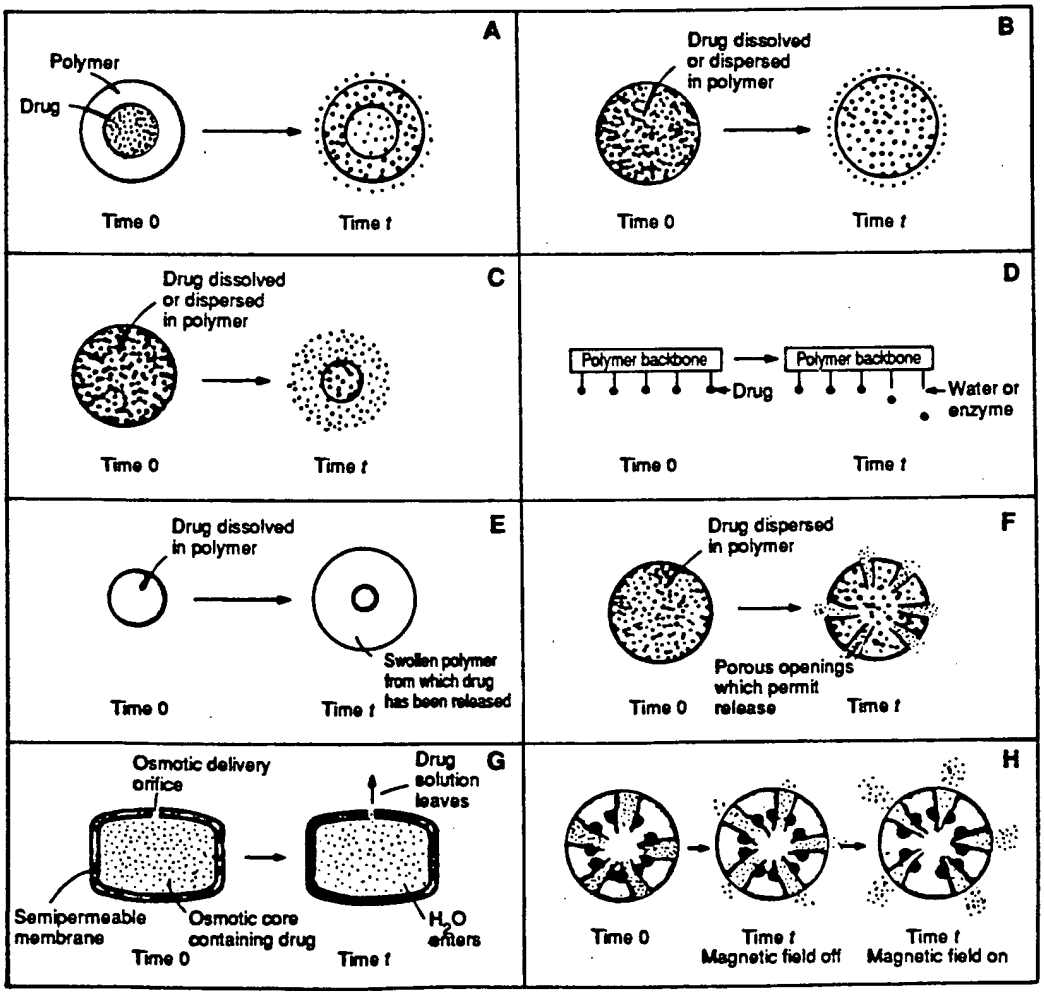

Fig. 1. Polymer release mechanisms. The most common release mechanism is diffusion, whereby the drug migrates from its initial position in the polymeric system to the polymer's outer surface and then to the body. Diffusion may occur through a reservoir (**A**), in which a drug core is surrounded by a polymer film, or in a matrix (**B**), where the drug is uniformly distributed through the polymeric system. Drugs can also be released by chemical mechanisms such as degradation of the polymer (**C**) or cleavage of the drug from a polymer backbone (**D**). Exposure to a solvent can also activate drug release. For example, the drug may be locked into place by polymer chains, and, upon exposure to environmental fluid, the outer polymer regions begin to swell, allowing the drug to move outward (**E**), or water may permeate a drug-polymer system as a result of osmotic pressure, causing pores to form and bringing about drug release (**F**). An attractive osmotic system that can provide constant release rates exists in the form of a pill that has a laser-drilled hole in the surface of a polymer coating (**G**). Some polymer systems can be externally activated to release more drug when needed, using forces such as magnetism (**H**). In this case, an external magnetic field causes polymer-embedded magnetic beads to "squeeze" drug-containing pores, forcing more drug out of a matrix. In all cases, dots represent drug, and in (H) the large dots represent magnetic beads. Combinations of the above mechanisms are possible. Release rates from polymer systems can be controlled by the nature of the polymeric material (for example, crystallinity or pore structure for diffusion-controlled systems; the lability of the bonds or the hydrophobicity of the monomers for chemically controlled systems) and the design of the system (for example, thickness and shape). The advantage of having systems with different release mechanisms is that each can accomplish different goals. For example, reservoir systems are able to produce near-constant release rates, whereas matrix systems are inexpensive to manufacture. Chemically controlled systems generally result in elimination of the polymer, whereas solvent-activated systems have release rates independent of pH (*50*).

target locally at a rate of approximately 65 μg/day, lasts for over 1 year; and (iv) vaginal rings, which are silicone reservoir systems used for 3 to 6 months; generally, for each monthly cycle they are inserted for 3 weeks and then are withdrawn for 1 week (*18*).

Tetracycline, incorporated into diffusion-controlled systems composed of ethylene–vinyl acetate copolymer or other substances, has been used to treat periodontal disease. When this controlled release system was placed in the periodontal pocket, significant reductions in bacterial counts and in the incidence of gingivitis were observed. Furthermore, because the systems are placed next to their target, treatment is accomplished with less than one-thousandth of the normal systemic dose (*19*).

A number of other controlled release systems are under study. These include localized release of diphosphonates (calcium chelators) to prevent heart valve calcification, dopamine or bromocriptine for potential treatment of Parkinson's disease, and bethanecol for potential treatment of Alzheimer's disease (*20*).

Controlled Release Systems for Peptides and Proteins

For many years, controlled-release systems were capable of slowly releasing drugs of only low molecular weight (<600). Large molecules such as proteins were not considered feasible candidates, because polypeptides were considered too large to slowly diffuse through most polymeric materials, even after swelling of the polymer. Large molecules could diffuse through highly porous membranes such as Millipore filters or certain gels such as polyacrylamide; however, in these cases, diffusion was generally too rapid to be of value and tissue damage was usually observed. The discovery that matrices of solid hydrophobic polymers containing powdered macromolecules enabled molecules of nearly any size to be released for over 100 days permitted controlled delivery of a variety of proteins, polysaccharides, and polynucleotides (*21*). Examples of polymers that perform in this way are nondegradable ethylene–vinyl acetate copolymer and degradable lactic acid–glycolic acid copolymers. Certain hydrogels such as poly(hydroxyethylmethacrylate) or poly (vinylalcohol) also work effectively but release proteins for shorter time periods than the above polymer systems.

The release mechanism generally involves movement of the polypeptide through a complex porous path in the polymer matrix. If the polymer erodes, this will affect the pore structure and accelerate the release. Factors influencing release rates include protein particle size and loading, protein solubility and molecular weight, polymer composition and molecular weight, and the dimensions and shape of the matrix (*22*). Polymer systems are now being used in animal studies to release many proteins, including insulin, growth factors, and angiogenesis inhibitors (*23*). The first Food and Drug Administration (FDA)–approved system for controlled release of a peptide, the Lupron Depot (injectable microspheres composed of lactic acid–glycolic acid copolymer and leuprolide acetate, and lasting 30 days) was recently introduced for the treatment of prostate cancer. Other polymeric systems for releasing similar drugs (*24*) are also under evaluation for treating endometriosis and other conditions.

A number of challenges in protein delivery remain. Foremost among these is that, when encapsulated proteins remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C. This can cause a loss of biological activity and possible changes in immunogenicity. Stabilization approaches being developed in protein chemistry (*25*) will be important for the success of some of these delivery systems. In one study that used solid proteins as a model, small amounts of added water induced aggregation of albumin, ovalbumin, glucose oxidase, and β-lactoglobulin. The aggregation as a function of added water went through a maximum with just 3 μl of water, causing 97% aggregation of 10 mg of albumin in 24 hours. At lower and higher water concentrations, aggregation was reduced. The aggregation mechanism was discovered to be intermolecular S–S bond formation through thiol-disulfide interchange. This, in turn, suggested rational strategies for protein stabilization, including modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions (*26*). In a study of ribonuclease, oxygen was responsible for protein aggregation (*27*).

Transdermal Controlled Release Systems

The skin is often considered a barrier that keeps all agents, including drugs, out of the body. However, a few drugs have just the right properties to penetrate the skin at appreciable rates and are potent enough so that only low doses are required. Furthermore, compared to the oral route, losses due to liver metabolism are reduced. The rate-limiting barrier to drug entry through the skin is the outermost skin layer, the stratum corneum, which is composed primarily of keratin and lipids. For a drug to penetrate the skin significantly, it should have a low molecular weight and appreciable solubility in both water and oil.

The first transdermal delivery system introduced clinically released scopolamine from patches (reservoir systems) to prevent nausea associated with motion sickness. After the patch has been applied, a 4- to 6-hour lag period is required for the drug to reach therapeutic concentrations. Because of the small amount of drug required (7 μg/hour over 3 days) and the high skin permeability of scopolamine, this system can be designed so that the device rather than the skin is rate-controlling. This minimizes patient to patient variations. The device is placed behind the ear because the permeability of the stratum corneum there is comparatively high, which further enables the device, rather than the skin, to provide the principal diffusion barrier.

The most widely used transdermal systems release nitroglycerin daily for the treatment of heart disease. These systems, first introduced in 1982, have annual sales of approximately $500 million. The amount of nitroglycerin absorbed is determined by the skin rather than the device; nitroglycerin patches of different sizes are available so that patients can select the desired dosages. However, the continuous delivery of nitroglycerin may create drug tolerance. The possibility of controlled intermittent delivery of nitroglycerin is being explored.

A weekly clonidine patch and a twice weekly estradiol patch are used to treat hypertension and estradiol deficiency (for postmenopausal females), respectively. There have been reports of local irritation with these systems, perhaps because of their longer application periods or because of the combined effects of bioadhesives, chemicals, and drugs used in the formulations. Transdermal systems for the delivery of testosterone, fentanyl, isosorbide dinitrate, nicotine, timolol, and antihistamines, although not yet clinically available, are under study.

The biggest challenge in transdermal delivery is to increase the variety of drugs that can be administered. Four approaches have been explored. Electrical means such as iontophoresis, which can drive charged molecules through the skin, have received considerable attention. It has been proposed that iontophoresis might allow the transdermal delivery of larger molecular weight drugs, such as insulin. Animal studies with insulin have not led to conclusive results; insulin permeation depends on the animal model, the type of

current, and whether the stratum corneum has been removed (*28*). Nonetheless, clinical studies have shown that smaller peptides such as luteinizing hormone–releasing hormone (LHRH) can be delivered at increased rates (*29*). A second approach uses ultrasound to enhance transdermal drug permeation. Ultrasound also eliminates the lag times associated with transdermal drug delivery in animal models (*30*). Chemical modification provides a third approach: a lipophilic drug could be synthesized that penetrates the skin and is subsequently converted by epidermal enzymes into the original drug. Finally, penetration enhancers such as Azone, dimethyl sulfoxide, and dimethyl formamide have been used. However, extensive testing must be done to establish safety. It may be more useful to utilize agents used in FDA-approved topical formulations (for example, ethanol is used in the estradiol system to enhance penetration).

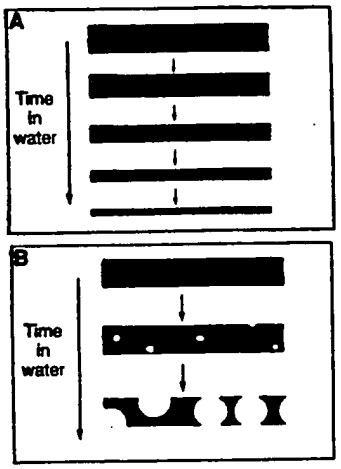

Fig. 2. Idealized diagram of polymer matrices displaying surface erosion (**A**) or bulk erosion (**B**).

Novel Degradable Polymers

Most materials used in medicine today were not designed for biomedical applications. For example, the polymers used in the artificial heart and dialysis tubing were originally used in ladies' girdles and sausage casings, respectively. These materials were chosen because they appeared, to some extent, to resemble the organs they were intended to replace. A significant challenge is to develop more rational approaches for creating improved materials for humans. This may be particularly important in the development of degradable polymers.

For such polymers, to maximize control over release, it is often desirable for a system to degrade only from its surface (Fig. 2A). [The only degradable polymers in common use, polyesters such as lactic acid–glycolic acid copolymers, display bulk (homogeneous) erosion (Fig. 2B), resulting in significant degradation in the matrix interior.] For surface-eroding systems, the drug release rate is proportional to the polymer erosion rate. This eliminates the possibility of dose dumping, improving device safety; release rates can be controlled by changes in system thickness and total drug content, facilitating device design. Achieving surface erosion requires that the degradation rate on the polymer matrix surface be much faster than the rate of water penetration into the matrix bulk. Efforts have begun to design such ideal polymers. Theoretically, the polymer should be hydrophobic but should have water-labile linkages connecting monomers.

It was proposed that, because of the lability of anhydride linkages, polyanhydrides would be a promising class of polymers. By varying the monomer ratios in polyanhydride copolymers, surface-eroding polymers lasting from 1 week to several years were designed and synthesized (*31*).

The possibility of implanting polyanhydride disks containing nitrosoureas for treating brain cancer after surgery is being explored. Normally, nitrosoureas are given intravenously (they have a half-life of 12 to 15 min and cause serious toxicity to several organs). By placing nitrosoureas in polyanhydrides, the drug is protected and its efficacy lasts approximately for the duration of the polymer lifetime (in this case, nearly 1 month). The polymer disks also deliver the drug locally to the brain, significantly reducing systemic toxicity. Surface erosion is desirable, for, if bulk erosion were to occur, uncontrolled amounts of this potentially toxic drug could be released during breakup of the matrix. These polymers have been shown to be safe in numerous animal models (*32*). Institutional Review Board approval was then obtained to conduct clinical trials with polyanhydrides at five U.S. hospitals. In 1987, the FDA approved these polyanhydrides for clinical trials. In an initial study of 21 patients, safety was demonstrated and patient lifetime was extended significantly beyond that afforded by conventional treatments (*33*). A phase-3 trial involving 32 hospitals is currently under way; over 100 patients have been treated.

Several different surface-eroding polyorthoester systems have been synthesized. In this case, additives are placed inside the polymer matrix, which causes the surface to degrade at a different rate than the rest of the matrix. Such a degradation pattern can occur because these polymers erode at very different rates, depending on pH, and the additives maintain the matrix bulk at a pH different from that of the surface. By varying the type and amount of additive, release rates can be controlled (*34*).

It may be desirable to have degradable polymers that consist of, and break down into, naturally occurring metabolites. Thus, new polyamino acids were synthesized in which L-amino acids or dipeptides were polymerized by nonamide bonds between functional groups (for example, esters) located on amino acid side chains. This approach permits the synthesis of biomaterials (for drug delivery systems, artificial organs, vascular grafts, or other prostheses) that are derived from nontoxic substances, which also have other desirable properties: (i) the incorporation of an anhydride linkage into the polymer backbone causes rapid degradability; (ii) an ester bond provides better film and fiber formation; and (iii) an imide or iminocarbonate bond improves mechanical strength (*35*).

One such polymer is being studied in vaccine delivery. Many adjuvants such as aluminum oxide or Freund's adjuvant rely on a simple "depot" effect, releasing antigen over a short period, from several hours to a few weeks. In earlier studies in mice and rabbits, prolonged release of small amounts of antigen from a nondegradable device resulted in sustained antibody production for over 6 months (*36*). Although these studies demonstrated the potential value of controlled release in immunization, it would be advantageous to use degradable systems to avoid implant retrieval. This concept is particularly attractive, because the polymer degradation products could be intentionally designed to have adjuvant properties, that is, an "engineered" polymer. This would permit the design of a system that could stimulate the immune response while simultaneously releasing antigen over long periods. Because of the adjuvanticity of L-tyrosine and its derivatives, a polymer consisting of tyrosine or a tyrosine derivative connected by hydrolyzable iminocarbonate bonds was synthesized. When this polymer was converted into small pellets, this system provided sustained adjuvanticity while simultaneously serving as an antigen repository. The release of antigen from a single tyrosine-based polyiminocarbonate pellet gave rise, in mice, to higher antibody titers than release of the same antigen dose from a control polyiminocarbonate pellet or from two injections of the antigen over 1 year (*37*).

Pulsatile Polymeric Controlled Release Systems

It would be desirable if polymeric systems could be designed to release increased levels of drug when needed; this would mimic the body's physiological processes. Both open-loop and closed-loop approaches are being studied. One open-loop system contains drug and small magnetic beads embedded in a polymer matrix (Fig. 1H). Release rates are enhanced when desired by an oscillating external magnetic field. Parameters that affect the release rate include the magnetic field frequency and strength, the polymer composition, and the strength and orientation of the polymer-embedded magnets. Application of the magnetic field causes up to 30-fold increases in release rates (*38*). Ultrasound can also be used to enhance drug release rates from polymers (*39*). Successful clinical implementation of the ultrasonic or magnetic systems will probably require the creation of small portable triggering devices (wristwatch size) that can be preprogrammed or activated manually when desired.

Several closed-loop polymeric systems are being developed. In one case intended for the increased release of insulin in the presence of excess glucose, glucose oxidase was immobilized within an insulin-containing polyamine membrane. Glucose oxidase converts glucose to gluconic acid; the acid protonates amine groups within the membrane. The electrostatic repulsion of the positively charged amine groups causes expansion of the membrane and increased delivery of insulin. As the physiologic glucose concentration decreases in response to the released insulin, the membrane contracts, decreasing the rate of insulin release (*40*). In another approach, glucose oxidase was immobilized to agarose beads contained within a polymer matrix. The acid formed when external glucose reacts with the immobilized enzyme lowers the pH, which changes the solubility of insulin and the diffusional driving force. Increased release rates to glucose challenges were observed in vitro and in diabetic rats (*41*). A third approach involves the synthesis of glycosylated insulin bound to concanavalin A (Con A). Con A is immobilized on Sepharose beads. The glycosylated insulin is displaced from Con A in response to glucose, which competes for the same binding sites. The rate of insulin release also depends on the binding affinity of the insulin derivative to Con A and can be influenced by the choice of saccharide group in glycosylated insulin. By encapsulating glycosylated insulin-bound Con A within a suitable polymer that is permeable to both glucose and insulin, it is possible to control glucose influx and insulin efflux (*42*). Critical issues with respect to each of these delivery systems are the stability of insulin and enzymes and the rapidity of movement (response time) of insulin from the polymer matrix to the circulation. Such systems may also benefit from ongoing research in biosensors (*43*).

Research is being conducted on self-triggered release of drugs such as narcotic antagonists in multicomponent systems involving erodible polymers, antibodies, and enzymes (*44*). Pulsatile systems involving pH-sensitive or temperature-sensitive polymers are also being studied, as are polymer systems that can be activated by light or electricity (*45*).

Conclusions and Future Directions

The studies discussed here show that carriers can affect drug level, location, longevity, and antigenicity. Although this technology is at an early stage, it has already made a significant clinical and commercial impact. This technology is not limited to medicine. Controlled release has been used for pet flea collars, pesticides, anti-fouling agents, fertilizers, and fragrances. Liposomes are used in cosmetics.

There are numerous challenges ahead. One area is the creation of bioadhesive polymers that could alter a drug's location when given orally (*46*). This could be particularly important for drugs that are absorbed only in certain segments of the gastrointestinal tract. Even more tantalizing, but more difficult, is delivering large and complex molecules such as proteins orally. Research on novel anatomical delivery pathways such as the nose or lung may also permit the delivery of a wider spectrum of drugs. Furthermore, an understanding of cell transport mechanisms may aid in cellular targeting (*47*).

Although this article has focused principally on specific carriers for pharmaceuticals, ongoing research in cell transplantation could be used to provide desired agents (*48*). The possibility of inserting genes into cells to produce desired entities is being explored (*49*).

Furthermore, continuous advances in biotechnology will have at least several major effects on drug delivery. First, novel complex drugs will be created that will be difficult to administer by conventional means. Second, approaches being developed in genetic engineering may enable the creation of new molecular constructs (for example, deletion mutants, hybrid proteins, and ligated gene fusion hybrids) with increased ability to achieve site-specific delivery. Finally, advances in materials science and chemical engineering should permit improved polymers, lipids, antibodies, and other substances to be synthesized, better understood, manufactured, and effectively used in drug delivery.

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Molecular Targets for AIDS Therapy

HIROAKI MITSUYA, ROBERT YARCHOAN, SAMUEL BRODER

The development of antiretroviral therapy against acquired immunodeficiency syndrome (AIDS) has been an intense research effort since the discovery of the causative agent, human immunodeficiency virus (HIV). A large array of drugs and biologic substances can inhibit HIV replication in vitro. Nucleoside analogs—particularly those belonging to the dideoxynucleoside family—can inhibit reverse transcriptase after anabolic phosphorylation. 3′-Azido-2′,3′-dideoxythymidine (AZT) was the first such drug tested in individuals with AIDS, and considerable knowledge of structure-activity relations has emerged for this class of drugs. However, virtually every step in the replication of HIV could serve as a target for a new therapeutic intervention. In the future, non-nucleoside–type drugs will likely become more important in the experimental therapy of AIDS, and antiretroviral therapy will exert major effects against the morbidity and mortality caused by HIV.

HUMAN IMMUNODEFICIENCY VIRUS (HIV) IS A PATHOgenic retrovirus and the causative agent of acquired immunodeficiency syndrome (AIDS) and its related disorders. One of the central questions after HIV was discovered was whether antiretroviral therapy would ever be feasible. Since that time, one drug, 3′-azido-2′,3′-dideoxythymidine (AZT or zidovudine) (*1*) has been shown to prolong the survival and improve the quality of life of individuals with advanced HIV infection (*2, 3*). More recently, the administration of AZT was shown to delay clinical progression in certain asymptomatic individuals with HIV infection (*4*). Thus, the central question now is no longer whether antiretroviral therapy will be feasible, but rather, how to use the emerging knowledge of the viral life cycle to create new opportunities for therapy.

The purpose of this review is to discuss some principles for the development of antiretroviral drugs in the therapy of HIV infection and to highlight some recent advances in this area. Successful antiviral drugs, in theory, exert their effects by interacting with viral receptors, virally encoded enzymes, viral structural components, viral genes or their transcripts, or cellular factors required for viral

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For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 *bis* 1 and 90 *bis* 3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ALYSIA BERMAN Telephone No. (703) 308-0196

Form PCT/ISA/220 (January 1994)*

(See notes on accompanying sheet)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/20114

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/16
US CL :424/493, 494, 497

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/493, 494, 497

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,780,055 A (HABIB et al.) 14 July 1998, abstract, col. 2, col. 9, lines 42-45, col. 22, lines 28-33, col. 32, lines 5 and 10-13, col. 36, lines 16-17.	1, 4-14
A	US 4,874,613 A (HSIAO) 17 October 1989.	1-14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 15 OCTOBER 1999	Date of mailing of the international search report 17 NOV 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ALYSIA BERMAN Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)★

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

RECEIVED
1999 NOV 29 AM 10:32
WELSH & KATZ, LTD.

To: EDWARD P. GAMSON
WELSH & KATZ, LTD.
120 SOUTH RIVERSIDE PLAZA
22ND FLOOR
CHICAGO, IL 60606

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

	Date of Mailing *(day/month/year)* 22 NOV 1999
Applicant's or agent's file reference ASC-110.0 PC	FOR FURTHER ACTION **See paragraphs 1 and 4 below**
International application No. PCT/US99/20113	International filing date *(day/month/year)* 01 SEPTEMBER 1999
Applicant ASCENT PEDIATRICS, INC.	

1. [X] The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 *bis* 1 and 90 *bis* 3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer BRIAN K. SEIDLECK
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference ASC-110.0 PC	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US99/20113	International filing date *(day/month/year)* 01 SEPTEMBER 1999	(Earliest) Priority Date *(day/month/year)* 03 SEPTEMBER 1998
Applicant ASCENT PEDIATRICS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (See Box I).

2. [ ] **Unity of invention is lacking** (See Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] transcribed by this Authority.

4. With regard to the **title**,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference ASC-111.0 PC	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US99/20114	International filing date *(day/month/year)* 01 SEPTEMBER 1999	(Earliest) Priority Date *(day/month/year)* 03 SEPTEMBER 1998
Applicant ASCENT PEDIATRICS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

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   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] transcribed by this Authority.

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   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/20113

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/20, 9/16

US CL :424/451, 456, 457, 458, 461, 462, 489, 493, 494, 497

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/451, 456, 457, 458, 461, 462, 489, 493, 494, 497

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,780,055 A (HABIB et al) 14 July 1998, see entire document.	1-15
Y	US 4,874,613 A (HSIAO) 17 October 1989, see entire document.	1-15
Y	US 5,773,031 A (SHAH et al) 30 June 1998, see entire document.	1-15
Y	US 4,867,984 A (PATEL) 18 September 1989, see entire document.	1-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

05 NOVEMBER 1999

Date of mailing of the international search report

22 NOV 1999

Name and mailing address of the ISA/US
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Washington, D.C. 20231

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Form PCT/ISA/210 (second sheet)(July 1992)★